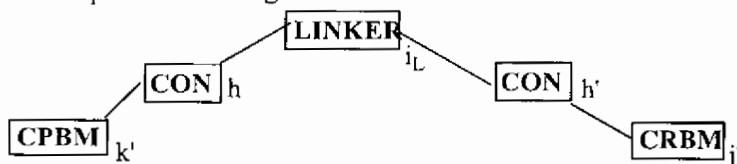


EXHIBIT 12

Claims:

1. A bifunctional compound according to the chemical structure:



Wherein [CPBM] is a Circulating Protein Binding Moiety which binds to a circulating protein which mediates a disease state and/or condition and is to be removed by the action of hepatocytes or other cells on the circulating protein (the compounds preferably selectively binding to the CPBM in plasma of the subject or patient);

[CRBM] is a cellular receptor binding moiety which binds to hepatocytes or other degrading cells through asialoglycoprotein receptors of hepatocytes or other cell receptors which are on the surface degrading cells in a patient or subject;

Each [CON] is an optional connector chemical moiety which, when present, connects directly to [CPBM] or to [CRBM] or connects the [LINKER] to [CPBM] or to [CRBM] and

[LINKER] is a chemical moiety having a valency from 1 to 15, 1 to 10, 1 to 5 or 1, 2 or 3, which covalently attaches to one or more [CRBM] and/or [CPBM] group, optionally through a [CON], including a [MULTICON] group, wherein said [LINKER] optionally itself contains one or more [CON] or [MULTICON] group(s);

k' is 1 to 15, 1 to 10, 1 to 5, 1 to 3 or 1, 2 or 3;

j' is 1 to 15, 1 to 10, 1 to 5, 1 to 3 or 1, 2 or 3;

h and h' are each independently 0 to 15, 1 to 15, 1 to 10, 1 to 5, 1 to 3 or 1, 2 or 3;

i_L is 0 to 15, 1 to 15, 1 to 10, 1 to 5, 1 to 3, or 1, 2 or 3, preferably i_L is 1 to 5 or 1, 2 or 3 with the proviso that at least one of h , h' and i_L is preferably at least 1, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

2. The compound according to claim 1 wherein k' , j' , h , h' and i_L are each independently 1, 2 or 3.
3. The compound according to claim 1 or 2 wherein k' is 1 and j' is 1, 2 or 3.
4. The compound according to claim 1 according to any of claims 1-3 wherein [CPBM] is a [MIFBM] moiety according to the chemical structure:

EXHIBIT 13

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:

DOYLE, Kathryn
Saul Ewing Arnstein & Lehr LLP
Center Square West
1500 Market Street, 38th Floor
Philadelphia, PA 19102
United States of America

Date of mailing (day/month/year)
15 August 2019 (15.08.2019)

Applicant's or agent's file reference
Y03-182PCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US 2019/026260

International filing date (day/month/year)
08 April 2019 (08.04.2019)

Applicant
YALE UNIVERSITY

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau of WIPO, preferably through ePCT or on paper to, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of **18 months from the priority date**, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **22 months from priority date**, the applicant may request that a **supplementary international search** be carried out by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/RU:
Federal Institute of Industrial Property,
Berezhkovskaya nab., 30-1, Moscow, G-59,
GSP-3, Russia, 125993
Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37

Authorized officer



T. Vladimirova

Telephone No. 499-240-25-91

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference Y03-182PCT	FOR FURTHER ACTION		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 2019/026260	International filing date (<i>day/month/year</i>) 08 April 2019 (08.04.2019)	(Earliest) Priority Date (<i>day/month/year</i>) 09 April 2018 (09.04.2018)	
Applicant YALE UNIVERSITY			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 31
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 31 contains a reference to the drawings in relation to the technical features of the invention, that contrary to in accordance with PCT Rule 6.2 (a).

3. ☒ Claims Nos.: 4-30
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER <div style="text-align: right;">(see extra sheet)</div> <p>According to International Patent Classification (IPC) or to both national classification and IPC</p>		
B. FIELDS SEARCHED <p>Minimum documentation searched (classification system followed by classification symbols)</p> <p style="text-align: center;">A61K 45/06, 47/55, 47/64, 31/351, C07D 309/10, A61P 35/00, 29/00, 37/00</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)</p> <p style="text-align: center;">PatSearch (RUPTO Internal), USPTO, PAJ, Espacenet, Google</p>		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2016/0082112 A1 (YALE UNIVERSITY) 24.03.2016, claims, [0121], [0166], [0169]	1-3, 32-45
Y	STOKMAIER Daniela. Targeting Hepatocytes via the Asialoglycoprotein-Receptor. Inaugural dissertation, Basel, 14 December 2010, pp. 3-140, 3-141, 3-142, 3-143, 3-149, fig. 65, 67	1-3, 32-45
Y	US 2016/0207953 A1 (PFIZER INC.) 21.07.2016, claims, [0028], [0054], [0068], [0087] - [0088], [0215]	1-3, 32-45
Y	ROSENG Lars et al. Uptake, intracellular transport, and degradation of polyethylene glycol-modified asialofetuin in hepatocytes. The Journal of Biological Chemistry, 1992, 267(32): pp. 22987-2293	1-3, 32-45
Y	WO 2016/040305 A1 (TEMPLE UNIVERSITY-OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION) 17.03.2016, claims, fig. 13A, C, 21	1-3, 32-45
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
*	Special categories of cited documents:	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention “X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone “Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art “&” document member of the same patent family
“A”	document defining the general state of the art which is not considered to be of particular relevance	
“E”	earlier document but published on or after the international filing date	
“L”	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
“O”	document referring to an oral disclosure, use, exhibition or other means	
“P”	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search		Date of mailing of the international search report
15 July 2019 (15.07.2019)		15 August 2019 (15.08.2019)
Name and mailing address of the ISA/RU: Federal Institute of Industrial Property, Berezhkovskaya nab., 30-1, Moscow, G-59, GSP-3, Russia, 125993 Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37		Authorized officer S. Ilchenko Telephone No. (8-499) 240-25-91

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ZHANG Yingnan et al. Identification of a Small Peptide That Inhibits PCSK9 Protein Binding to the Low Density Lipoprotein Receptor. The Journal Biological Chemistry, 2014; 289(2): pp. 942-955	1-3, 32-45
Y	FAIRBROTHER Wayne J. et al. Novel Peptides Selected to Bind Vascular Endothelial Growth Factor Target the Receptor-Binding Site. Biochemistry, 1998, 37(51): pp. 17754-17764	1-3, 32-45
Y	LANDRY James P. et al. Discovering small molecule ligands of vascular endothelial growth factor that block VEGF-KDR binding using label-free microarray-based assays. Assay and Drug Development Technologies, 2013, 11(5): pp. 326-332	1-3, 32-45
Y	RIBEIRO Solange M.F. et al. The Activation Sequence of Thrombospondin-1 Interacts with the Latency-associated Peptide to Regulate Activation of Latent Transforming Growth Factor- β . The Journal Biological Chemistry, 1999, 274(19): pp. 13586-13593	1-3, 32-45
Y	BURMESTER James K. et al. Small Molecule Antagonists of the TGF- β 1/TGF- β Receptor Binding Interaction. Medical Oncology, 2006, 23(4): pp. 553-562	1-3, 32-45
Y	RULLO Anthony F. et al. Re-engineering the Immune Response to Metastatic Cancer: Antibody-Recruiting Small Molecules Targeting the Urokinase Receptor. Angew Chem Int Ed, 2016, 55(11): pp. 3642-3646	1-3, 32-45
Y	BRAISTED Andrew C. et al. Discovery of a Potent Small Molecule IL-2 Inhibitor through Fragment Assembly. J. Am. Chem. Soc. 2003, 125(13): pp. 3714-3715	1-3, 32-45
Y	PARKER Christopher G. et al. Illuminating HIV gp120-ligand recognition through computationally-driven optimization of antibody-recruiting molecules. Chem. Sci., 2014, 5(6): pp. 2311-2317	1-3, 32-45

INTERNATIONAL S
Classification of

No.
/US 2019/026260

A61K 45/06 (2006.01)
A61K 47/55 (2017.01)
A61K 47/64 (2017.01)
A61K 31/351 (2006.01)
C07D 309/10 (2006.01)
A61P 35/00 (2006.01)
A61P 29/00 (2006.01)
A61P 37/00 (2006.01)

PCT**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**(PCT Rule 43*bis*.1)

DOYLE, Kathryn
Saul Ewing Arnstein & Lehr LLP, Center Square West,
1500 Market Street, 38th Floor
Philadelphia, PA 19102
United States of America

Date of mailing (*day/month/year*)
15 August 2019 (15.08.2019)

Applicant's or agent's file reference
Y03-182PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US 2019/026260

International filing date (*day/month/year*)
08 April 2019 (08.04.2019)

Priority date (*day/month/year*)
09 April 2018 (09.04.2018)

International Patent Classification (IPC) or both national classification and IPC
(see extra sheet)

Applicant
YALE UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability;
citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/RU:
Federal Institute of Industrial Property,
Berezhkovskaya nab., 30-1, Moscow, G-59,
GSP-3, Russia, 125993
Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37

Date of completion of this opinion
15 July 2019 (15.07.2019)

Authorized officer
S. Ilchenko
Telephone No. (8-499) 240-25-91

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 4-31
because:
- ☐ the said international application, or the said claims Nos. _____ relate to the following
subject matter which does not require an international search (*specify*):

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 31
are so unclear that no meaningful opinion could be formed (*specify*):
Claim 31 contains a reference to the drawings in relation to the technical features of the invention,
that contrary to in accordance with PCT Rule 6.2 (a).

- ☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

- ☒ no international search report has been established for said claims Nos. 4-30
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the
International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with
the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the
Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner
acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative
Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under
Rule 13*ter*.1(a) or (b).
- ☐ See Supplemental Box for further details.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-3, 32-45	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-3, 32-45	NO
Industrial applicability (IA)	Claims	1-3, 32-45	YES
	Claims		NO

2. Citations and explanations:

D1: US 2016082112 A1, 24.03.2016.

D2: D. STOKMAIER. "Targeting Hepatocytes via the Asialoglycoprotein-Receptor". Inaugural dissertation, Basel, 14 December 2010, p.3-140, 3-141, 3-142, 3-143, 3-149, fig. 65, 67.

D3: US 2016207953 A1, 21.07.2016.

D4: ROSENG L. et al. "Uptake, intracellular transport, and degradation of polyethylene glycol-modified asialofetuin in hepatocytes." J Biol Chem. 1992; 267(32), p.22987-22993.

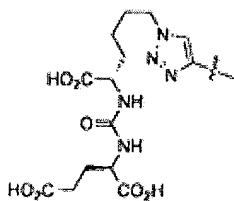
D1 is the closest prior art to the inventions according to claims 1, 32, 38, 39, 43-45.

D1 (claim 1) discloses the compound in accordance with the chemical structure:



where [IBT] is a FcγRI cell receptor binding fragment;

[CBT] is a cell-binding fragment that binds to the prostatic membrane antigen (PSMA), in particular a compound



Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of V:

PSMA is a soluble protein that is overexpressed in prostate cancer cells (par. [0166], [0169]), i.e. mediates a disease state, circulates in the plasma of the subject, and which should be removed.

L1 and L2 are linker groups that optionally include one or more bifunctional connector groups [CON];

[MULTICON] - a bifunctional or multifunctional group of connectors, which, if available, connects at least one group [IBT], at least one group [CBT] via a linker, i.e. [MULTICON] is a LINKER.

MCON (which corresponds to iL according to the present application) is an integer from 0 to 10;

NL1 and NL2 are integers from 0 to 10, provided that $n \geq NL1$ and $n' \geq NL2$ (which correspond to h, h', k' and j', respectively, according to the present application).

In some embodiments, D1 (the Claims) MCON is 1, 2 or 3, n is 1, 2 or 3, and n' is 1 or 2.

D1 (claims 30-48) also discloses a pharmaceutical composition comprising an effective amount of the abovementioned chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, as well as a method for treating prostate cancer in a patient in need thereof, including elucidating the introduction to the specified patient an effective amount of the compound. Additional anti-cancer agents, for example, cytarabine, alemtuzumab, etc., can be administered together with one or more chimeric compounds ([0121]).

The invention according to claims 1, 32, 38, 39, 43-45 differ from D1 in that instead of the [IBT] fragment that binds the cell receptor, where was used [CRBM], a fragment of the cell receptor that binds to hepatocytes or other degrading cells via asialoglycoprotein hepatocyte receptors or other cell receptors that are located on the surface of degrading cells in a patient or subject.

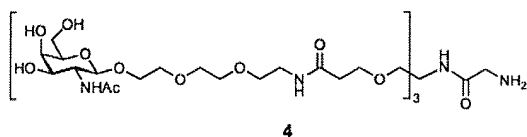
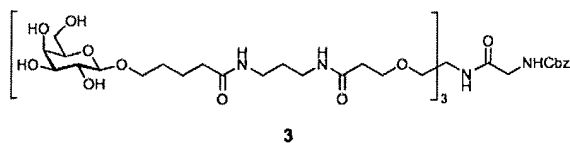
The inventions according to claims 44, 45 also differ in that they are aimed at treating an autoimmune or inflammatory disease.

Thus, the invention according to claims 1-3, 32-45 meets the novelty criteria.

However, D2 (p. 3-140, 3-141, Fig. 65) discloses "triatennary" compounds for binding to the asialoglycoprotein receptor (ASGP-R), in particular, having N-acetyl-D-galactose (GalNAc) as a carbohydrate ligand:

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of V:



Trivalent ligands for the asialoglycoprotein receptor (ASGP-R) (p.3-142, p.3-143, Fig.67, p.3-149) are synthetically readily available and hydrolytically stable. Both criteria are a prerequisite for their therapeutic use in the site-specific delivery of therapeutic agents (chemotherapeutic, DNA, etc.) for the liver.

GalNAc has been used successfully to target a wide range of drugs to the liver parenchyma and has high binding affinity for the ASGP-R receptor, especially when GalNAc is present in the multivalent state and when galactose residues are correctly located in space.

D3 (claims, [0087] - [0088], [0215]) discloses derivatives of substituted 6,8-dioxabicyclo [3.2.1] octane-2,3-diol, pharmaceutical compositions and their use as agents targeting the ASGP-R receptor present on the hepatocyte.

These derivatives can be conjugated to a system for the delivery of therapeutic agents to hepatocytes, for example, to PEG (poly (ethylene glycol) methyl ether) associated with a small molecule, an amino acid sequence, a nucleic acid sequence, an antibody, an oligomer, a polymer, genetically derived material, a liposome, a nanoparticle, dye, fluorescent probe (the Claims, par.[0054], [0068]).

The compounds of D3 ([0028]) can be used in a method for treating a disease or condition of the liver or a disease or condition modulated by the liver, including hyperglycemia similar to type II diabetes mellitus, primary sclerosing cholangitis and biliary atresia (autoimmune diseases), idiopathic neonatal hepatitis (inflammatory disease).

D4 (abstract, p. 22988, col. 1, par. 8) discloses the degradation of therapeutic compounds conjugated to a fragment that binds to the galactose hepatocyte receptor, resulting in the endocytic uptake of molecules and their decomposition.

Thus, D2 and D3 disclose various ligands that bind to the ASGP-R receptor to deliver various therapeutic compounds to hepatocytes where they degrade according to D4. In the light of D2 and D3, the specialist is motivated to use ligands targeting the ASGP-R receptor to deliver therapeutic

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of V:

agents to the liver, including as part of the chimeric compound of D1. It will be apparent to the person skilled in the art that replacing the FcγRI cell receptor binding fragment at D1 with a fragment that binds to the ASGP-R receptor at D2 or D3 in order to deliver the PSMA conjugate bound to hepatocytes for treating cancer.

The treatment of autoimmune and inflammatory diseases is obvious from D1-D3, since the PSMA binding fragment can be replaced by any other therapeutic agent, for example, known from D5-D13 (see below), for the treatment of the corresponding disease.

The features of dependent claims 2, 3, 33-37, 40 are known from D1 (claims, [0121]).
The features of dependent claims 41, 42 are known from D3 ([0028]).

Thus, the inventions according to independent claims 1, 32, 38, 39, 43-45 and dependent claims 2, 3, 33-37, 40-42 do not meet the criterion of inventive step.

The inventions according to claims 1-3, 32-45 meet the industrial applicability criteria.

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 31 contains a reference to the drawings in relation to the technical features of the invention, that contrary to in accordance with PCT Rule 6.2 (a).

Claim 33 contains a reference to itself that contrary to in accordance with the first sentence of PCT Rule 6.4 (a): any claim which includes all the features of one or more other claims (claim in dependent form, hereinafter referred to as "dependent claim") shall do so by a reference, if possible at the beginning, to the other claim or claims and shall then state the additional features claimed.

A61K 45/06 (2006.01)
A61K 47/55 (2017.01)
A61K 47/64 (2017.01)
A61K 31/351 (2006.01)
C07D 309/10 (2006.01)
A61P 35/00 (2006.01)
A61P 29/00 (2006.01)
A61P 37/00 (2006.01)

EXHIBIT 14

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: Kathryn Doyle
Saul Ewing Arnstein & Lehr LLP
1500 Market Street, 38th Floor
Centre Square West
Philadelphia, PA 19102

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) MAR 22 2021	
Applicant's or agent's file reference 047162-7250WO1	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US20/55078	International filing date (day/month/year) 09 October 2020 (09.10.2020)
Applicant Yale University	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau preferably through ePCT, or on paper to:
The International Bureau of WIPO, 34, chemin des Colombettes, 1211 Geneva 20, Switzerland

For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to any protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:**
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300
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Form PCT/ISA/220 (revised January 2020)

PCT**INTERNATIONAL SEARCH REPORT**

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 047162-7250WO1		FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US20/55078	International filing date (day/month/year) 09 October 2020 (09.10.2020)	(Earliest) Priority Date (day/month/year) 10 October 2019 (10.10.2019)	
Applicant Yale University			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1
☐ as suggested by the applicant.
☒ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
-***Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Groups I+, Claims 1-40, a compound encompassing Formula I, wherein the protein binder encompasses a moiety that binds to CD40L, as in claim 26, k' is 1, h, i, and h' are each 0; j' is 1, the CRBM encompasses folic acid (compound structure), and Addison's Disease (disease or disorder)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNA

4627

Application No.

PCT/US20/55078

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 35/407; A61K 39/395; C07D 475/04; C07K 14/705; C07K 14/725; C07K 16/28 (2020.01)

CPC - A61K 35/407; A61K 39/395; C07D 475/04; C07K 14/705; C07K 16/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	(NALAWANSHA, DA at al.) Targeted Protein Internalization and Degradation by ENDosome TARgeting Chimeras (ENDTACs). ACS Central Science, 9 May 2019, Vol. 5, No. 6; pages 1079-1084; abstract; page 1079, second column, second paragraph; page 1080, figures 1, 2A; DOI: 10.1021/acscentsci.9b00224	1, 5-6, 16-18, 31-35, 38-40 --- 26
Y	US 2007/0077197 A1 (WEDEKING, PW et al.) 5 April 2007; figures 8, 14A; paragraphs [0051], [0074], [0089]	1, 5-6, 16-18, 31-35, 38-40
Y	(D'SOUZA, AA et al.) Asialoglycoprotein receptor mediated hepatocyte targeting — Strategies and applications. Journal of Controlled Release, 10 April 2015, Epub 18 February 2015, Vol. 203; pages 126-139; abstract; DOI: 10.1016/j.jconrel.2015.02.022	16
Y	US 2004/0009907 A1 (ALSOBROOK II, JP et al.) 15 January 2004; paragraphs [0008], [0019], [0063], [0115], [0274], [0459], [1611], [1715], [1719], [1825], [1852], [2027], [2332]	31-35, 38-40
A	US 2007/0249682 A1 (ZHENG, Z et al.) 25 October 2007; abstract; paragraphs [0002], [0048], [0095]	26
A	US 2016/0362450 A1 (CARA THERAPEUTICS, INC.) 15 December 2016; figure 2; paragraph [0237]	26

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

04 March 2021 (04.03.2021)

Date of mailing of the international search report

MAR 22 2021

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

DEFS00050023

-Continued From Box No. III: Observations where unity of invention is lacking-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-40, a compound encompassing Formula I, wherein the protein binder encompasses a moiety that binds to CD40L, as in claim 26, k' is 1, h, i, and h' are each 0; j' is 1, the CRBM encompasses folic acid (compound structure), and Addison's Disease (disease or disorder) are directed toward compounds, compositions comprising the compounds, and methods associated therewith.

The compounds, compositions, and methods will be searched to the extent they encompass a compound encompassing Formula I, wherein the protein binder encompasses a moiety that binds to CD40L, as in claim 26, k' is 1, h, i, and h' are each 0; j' is 1, the CRBM encompasses folic acid (first exemplary compound structure), and Addison's Disease (first exemplary disease or disorder). Applicant is invited to elect additional compound(s), with fully specified structure(s) thereof, including, where applicable, specified SEQ ID NO: for each, such that the sequence and structure of each elected compound species is fully specified (i.e. no optional or variable atoms, bonds, residues or substituents), and/or additional disease(s) or disorder(s) to be searched. Additional compound(s) and/or disease(s) or disorder(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 5-6 (each in-part), 16-18 (each in-part), 26 (in-part), 31-35 (each in-part), and 38-40 (each in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound encompassing Formula I, wherein the protein binder encompasses a moiety that binds to CD40L, as in claim 26, k' is 1, h, i, and h' are each 0; j' is 1, the CRBM encompasses folic acid (compound structure), and Addison's Disease (disease or disorder). Applicants must specify the searchable claims that encompass any additionally elected compound(s) and/or disease(s) or disorder(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound encompassing Formula I, wherein the protein binder encompasses a moiety that binds to CD40L, as in claim 26, k' is 1, h, and h' are each 0; i is 1, and the linker encompasses a polyethylene glycol containing linker having 1-12 ethylene glycol residues; j' is 1, the CRBM encompasses folic acid (compound structure).

No technical features are shared between the compounds and/or diseases or disorders of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: a compound comprising formula (I), or a salt, geometric isomer, stereoisomer, or solvate thereof: [Protein binder]^{k'}-[CON]h-[Linker]i-[CON]h'-[CRBM]j' (I), wherein: the Protein binder is a molecule that binds to an extracellular protein; the CRBM is a cellular receptor binding moiety that binds to at least one receptor on the surface of a degrading cell in a subject, whereby binding of (I) leads to endocytosis and degradation of the extracellular protein; each CON is independently a bond or a group that covalently links a Protein binder to a CRBM, a Protein binder to a Linker, and/or a Linker to a CRBM; the Linker is a group having a valence ranging from 1 to 15; k' is an integer ranging from 1 to 15; h is an integer ranging from 0 to 15; i is an integer ranging from 0 to 15; h' is an integer ranging from 0 to 15; j' is an integer ranging from 1 to 15; a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound; and a method of treating, ameliorating, and/or preventing a disease or disorder in a subject, the method comprising administering a therapeutically effective amount of at least one compound.

However, these shared technical features are previously disclosed by US 2019/0000984 A1 to Regeneron Pharmaceuticals, Inc. (hereinafter 'Regeneron').

Regeneron discloses a compound comprising formula (I): [Protein binder]^{k'}-[CON]h-[Linker]i-[CON]h'-[CRBM]j' (I) (a multispecific antigen binding molecule comprising a first antigen binding domain, and a second antigen binding domain, wherein the antigen binding domains comprise covalently associated binding polypeptides (a compound comprising formula (I): [Protein binder]^{k'}-[CON]h-[Linker]i-[CON]h'-[CRBM]j' (I)); paragraphs [0004], [0040]), wherein: the Protein binder is a molecule that binds to an extracellular protein (wherein D1 binds to an extracellular, optionally soluble antigen (the Protein binder is a molecule that binds to an extracellular protein); Figure 1, paragraphs [0004], [0008]); the CRBM is a cellular receptor binding moiety that binds to at least one receptor on the surface (D2 binds to an internalizing antigen on the surface of a cell (the CRBM is a cellular receptor binding moiety that binds to at least one receptor on the surface); Figure 1B, paragraphs [0004], [0008], [0059]) of a degrading cell in a subject, whereby binding of (I) leads to endocytosis and degradation of the extracellular protein (of a degrading cell in a subject, whereby binding of (I) leads to endocytosis and degradation of the extracellular antigen (extracellular protein); paragraphs [0003], [0059]); a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound (pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound; paragraph [0084]); and a method of treating, ameliorating, and/or preventing a disease or disorder in a subject, the method comprising administering a therapeutically effective amount of at least one compound (a method of treating, ameliorating, and/or preventing sepsis (a disease or disorder) in a subject, the method comprising administering a therapeutically effective amount of at least one compound paragraphs [0085], [0118]).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Regeneron reference, unity of invention is lacking.

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: Kathryn Doyle Saul Ewing Arnstein & Lehr LLP 1500 Market Street, 38th Floor Centre Square West Philadelphia, PA 19102		Date of mailing (day/month/year) MAR 22 2021
Applicant's or agent's file reference 047162-7250WO1		FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/US20/55078	International filing date (day/month/year) 09 October 2020 (09.10.2020)	Priority date (day/month/year) 10 October 2019 (10.10.2019)
International Patent Classification (IPC) or both national classification and IPC IPC - A61K 35/407; A61K 39/395; C07D 475/04; C07K 14/705; C07K 14/725; C07K 16/28 (2020.01) CPC - A61K 35/407; A61K 39/395; C07D 475/04; C07K 14/705; C07K 16/28		
Applicant Yale University		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Date of completion of this opinion 04 March 2021 (04.03.2021)	Authorized officer Shane Thomas PCT Help Desk Telephone No. 571-272-4300
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Form PCT/ISA/237 (cover sheet) (revised January 2019)

DEFS00050025

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

~~International~~ application No.

PCT/US20/55078

Box No. 1	Basis of this opinion
1.	<p>With regard to the language, this opinion has been established on the basis of:</p> <p><input checked="" type="checkbox"/> the international application in the language in which it was filed.</p> <p><input type="checkbox"/> a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).</p>
2.	<p><input type="checkbox"/> This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(b)).</p>
3.	<p><input type="checkbox"/> With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of a sequence listing:</p>
a.	<p><input type="checkbox"/> forming part of the international application as filed:</p>
	<p><input type="checkbox"/> in the form of an Annex C/ST.25 text file.</p>
	<p><input type="checkbox"/> on paper or in the form of an image file.</p>
b.	<p><input type="checkbox"/> furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.</p>
c.	<p><input type="checkbox"/> furnished subsequent to the international filing date for the purposes of international search only:</p>
	<p><input type="checkbox"/> in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).</p>
	<p><input type="checkbox"/> on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).</p>
4.	<p><input type="checkbox"/> In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.</p>
5.	<p>Additional comments:</p>

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

application No.

PCT/US20/55078

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest and, where applicable, the protest fee.
 - ☐ paid additional fees under protest but the applicable protest fee was not paid.
 - ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

-Please See Supplemental Page--

4. Consequently, this opinion has been established in respect of the following parts of the international application:

☐ all parts.

☒ the parts relating to claims Nos. ***-Please See Supplemental Page-***-

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

application No.

PCT/US20/55078

Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement		
1.	Statement		
	Novelty (N)	Claims	1, 5-6, 16-18, 26, 31-35, 38-40
		Claims	NONE
			YES
			NO
	Inventive step (IS)	Claims	26
		Claims	1, 5-6, 16-18, 31-35, 38-40
			YES
			NO
	Industrial applicability (IA)	Claims	1, 5-6, 16-18, 26, 31-35, 38-40
		Claims	NONE
			YES
			NO
2.	Citations and explanations:		
	<p>Claims 1, 5-6 and 17-18 lack an inventive step under PCT Article 33(3) as being obvious over the publication entitled "Targeted Protein Internalization and Degradation by ENDosome TArgeting Chimeras (ENDTACs)" by Nalawansha, at al. (hereinafter "Nalawansha") in view of US 2007/0077197 A1 to Wedeking, et al. (hereinafter "Wedeking").</p> <p>As per claim 1, Nalawansha discloses a compound comprising formula I (as shown in figure 1, ENDTAC conjugate comprises extracellular protein of interest POI recruiting ligand linked to the cell surface receptor binding ligand; page 3, figure 1), wherein: the Protein binder is a molecule that binds to an extracellular protein (as shown in figure 1, the extracellular protein of interest POI recruiting ligand moiety binds to the extracellular protein of interest POI; page 3, figure 1); the CRBM is a cellular receptor binding moiety that binds to at least one receptor on the surface of a degrading cell (as shown in figure 1, the cell surface receptor binding ligand moiety binds G-protein coupled receptor GPCR on the surface of the cell that internalizes the complex with the attached protein of interest POI via endocytosis for lysosomal degradation, i.e., where the cell is the extracellular protein degrading cell; page 3, figure 1) in a subject (extracellular targets initiate aberrant signaling in cancer, i.e., where cancer is in the subject, we developed an approach to internalize extracellular proteins; abstract), whereby binding of I leads to endocytosis and degradation of the extracellular protein (as shown in figure 1, binding of ENDTAC conjugate to the GPCR on the cell surface, leads to internalization of the complex with the attached protein followed by endocytosis for lysosomal degradation of the extracellular protein of interest POI; page 3, figure 1); each CON is independently a bond that covalently links a Protein binder to an CRBM (as shown in figure 2A, in the ENDTAC conjugate covalent bond links the chloroalkyl moiety that targets extracellular POI to the cell surface receptor binding ligand; page 5, figure 2A); the Linker is a group having a valence 2 (as shown in figure 2A, the ENDTAC conjugate comprises a polyethylene glycol linker, one valency of which is attached to the chloroalkyl and the other one is to the cell surface receptor binding ligand; page 5, figure 2A); k' is 1 (as shown in figure 2A, the ENDTAC conjugate comprises one chloroalkyl moiety that targets extracellular POI, k' is 1; page 3, figure 1; page 5, figure 2A); h is 0 (as shown in figure 2A, in the ENDTAC conjugate the chloroalkyl moiety that targets extracellular POI is linked directly to the polyethylene glycol linker, h is 0; page 3, figure 1; page 5, figure 2A); h' is 0 (as shown in figure 2A, in the ENDTAC conjugate the surface receptor binding ligand moiety is linked directly to the polyethylene glycol linker, h' is 0; page 3, figure 1; page 5, figure 2A); j' is 1 (as shown in figure 2A, the ENDTAC conjugate comprises one cell surface receptor binding ligand moiety, j' is 1; page 3, figure 1; page 5, figure 2A). Nalawansha does not disclose wherein i is 0. However, Wedeking discloses wherein i is 0 (in conjugate 36 shown in figure 14A, the folic acid residue shown in paragraph [0089], is linked directly, i.e., i is 0, to two chelating ligands 17b having conjugable amino function and shown in protected form in figure 8; figures 8, 14A; paragraphs [0074], [0089]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Nalawansha, in order to have provided for wherein i is 0, as previously disclosed by Wedeking (Wedeking; figures 8, 14A; paragraphs [0074], [0089]), to adjust the structure of the conjugate to improve the properties of the conjugate in conducting targeted endocytosis of the protein of interest POI via lysosomal degradation (Nalawansha; page 3, figure 1). Further, provided that Nalawansha and Wedeking both disclose the use of the conjugates of the ligands targeting cell surface receptors to enhance the transport of the agents or compounds across the membrane of living cells through the receptor-mediated endocytosis (Nalawansha; abstract; page 3, figure 1; page 5, figure 2A) (Wedeking; paragraphs [0008], [0061]) targeting folate receptors (Nalawansha; folate receptor can be used to selectively deliver a wide range of therapeutic agents; page 1079, second column, second paragraph) (Wedeking; the composition comprises macrocyclic and non-macrocyclic ligands selectively coupled to folate-receptor binding ligands; paragraph [0051]), the modification to Nalawansha's compound, of providing for wherein i is 0, would provide the benefit of adjusting the structure of the conjugate to improve the properties of the conjugate in conducting targeted endocytosis of the protein of interest POI via lysosomal degradation (Nalawansha; page 3, figure 1).</p> <p>As per claim 5, Nalawansha and Wedeking, in combination, disclose the compound of claim 1, and Nalawansha further discloses wherein k' is 1 (as shown in figure 2A, the ENDTAC conjugate comprises one chloroalkyl moiety that targets extracellular POI, k' is 1; page 3, figure 1; page 5, figure 2A).</p> <p>As per claim 6, Nalawansha and Wedeking, in combination, disclose the compound of claim 1, and Nalawansha further discloses wherein j' is 1 (as shown in figure 2A, the ENDTAC conjugate comprises one cell surface receptor binding ligand moiety, j' is 1; page 3, figure 1; page 5, figure 2A).</p> <p>As per claim 17, Nalawansha and Wedeking, in combination, disclose the compound of claim 1, and in a separate embodiment Nalawansha further discloses wherein the CRBM is a folic acid folate receptor binder (folate receptor can be used to selectively deliver a</p>		
	-***-Continued in Supplemental Box-***-		

Form PCT/ISA/237 (Box No. V) (revised January 2019)

DEFS00050028

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

application No.

PCT/US20/55078

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1 and 6 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 1 and 6 are indefinite for the following reason(s): the formula of Claim 1 discloses a variable j' , where the description of variables in claims 1 and 6 discloses a variable j and does not disclose variable j' , which renders the claim indefinite. For examination purposes, variable j in the description will be interpreted as j' .

Claim 26 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 26 is indefinite for the following reason(s): Claim 26 refers to "wherein the Protein binder that binds to CD40L comprises", in line 2, where the preceding claim 1 does not disclose "binder that binds to CD40L". There is a lack of antecedent basis for these limitations in the claim. For the purpose of this opinion, as best understood, the claim is interpreted to read "wherein the Protein binder binds to CD40L and comprises".

Claim 26 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 26 is indefinite for the following reason(s): the first formula of Claim 26 discloses a moiety of Protein binder has two linking groups independently connected to the cyclohexyl and pyrrolidine moieties, thus linking Protein binder to at least two other moieties, where the preceding claim 1 discloses a formula in which k' is 1, h is 0, i is 0, h' is 0 and j' is 1, i.e., where one Protein binder is linked to one CRBM, which renders the claim indefinite. For examination purposes, an assumption was made that CRBM is attached to the Protein binder at either one cyclohexyl or pyrrolidine moiety, and the second unused moiety is linked to a hydrogen.

Claim 26 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 26 is indefinite for the following reason(s): the first formula of claim 26 discloses a compound comprising two instances of a methylene bridge connecting two pyrrolidine moieties, where the methylene bridge in each of these instances has a specific stereo-chemical configuration, where in each of these two instances two identical hydrogen atoms are attached to the carbon atom of the methylene bridge, which excludes fixed or determined stereo-chemical configurations of this moiety, which renders the claim indefinite. For examination purposes, the stereo-chemical configurations of the methylene bridges connecting two pyrrolidine moieties will be ignored.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

-Continued From Box IV (ii): Lack of unity of invention-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-40, a compound encompassing Formula I, wherein the protein binder encompasses a moiety that binds to CD40L, as in claim 26, k' is 1, h, i, and h' are each 0; j' is 1, the CRBM encompasses folic acid (compound structure), and Addison's Disease (disease or disorder) are directed toward compounds, compositions comprising the compounds, and methods associated therewith.

The compounds, compositions, and methods will be searched to the extent they encompass a compound encompassing Formula I, wherein the protein binder encompasses a moiety that binds to CD40L, as in claim 26, k' is 1, h, i, and h' are each 0; j' is 1, the CRBM encompasses folic acid (first exemplary compound structure), and Addison's Disease (first exemplary disease or disorder). Applicant is invited to elect additional compound(s), with fully specified structure(s) thereof, including, where applicable, specified SEQ ID NO: for each, such that the sequence and structure of each elected compound species is fully specified (i.e. no optional or variable atoms, bonds, residues or substituents), and/or additional disease(s) or disorder(s) to be searched. Additional compound(s) and/or disease(s) or disorder(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 5-6 (each in-part), 16-18 (each in-part), 26 (in-part), 31-35 (each in-part), and 38-40 (each in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound encompassing Formula I, wherein the protein binder encompasses a moiety that binds to CD40L, as in claim 26, k' is 1, h, i, and h' are each 0; j' is 1, the CRBM encompasses folic acid (compound structure), and Addison's Disease (disease or disorder). Applicants must specify the searchable claims that encompass any additionally elected compound(s) and/or disease(s) or disorder(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound encompassing Formula I, wherein the protein binder encompasses a moiety that binds to CD40L, as in claim 26, k' is 1, h, and h' are each 0; i is 1, and the linker encompasses a polyethylene glycol containing linker having 1-12 ethylene glycol residues; j' is 1, the CRBM encompasses folic acid (compound structure).

No technical features are shared between the compounds and/or diseases or disorders of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: a compound comprising formula (I), or a salt, geometric isomer, stereoisomer, or solvate thereof: [Protein binder]^{k'}-[CON]^h-[Linker]^j-[CON]^{h'}-[CRBM]^{j'} (I), wherein: the Protein binder is a molecule that binds to an extracellular protein; the CRBM is a cellular receptor binding moiety that binds to at least one receptor on the surface of a degrading cell in a subject, whereby binding of (I) leads to endocytosis and degradation of the extracellular protein; each CON is independently a bond or a group that covalently links a Protein binder to a CRBM, a Protein binder to a Linker, and/or a Linker to a CRBM; the Linker is a group having a valence ranging from 1 to 15; k' is an integer ranging from 1 to 15; h is an integer ranging from 0 to 15; i is an integer ranging from 0 to 15; h' is an integer ranging from 0 to 15; j' is an integer ranging from 1 to 15; a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound; and a method of treating, ameliorating, and/or preventing a disease or disorder in a subject, the method comprising administering a therapeutically effective amount of at least one compound.

However, these shared technical features are previously disclosed by US 2019/0000984 A1 to Regeneron Pharmaceuticals, Inc. (hereinafter 'Regeneron').

Regeneron discloses a compound comprising formula (I): [Protein binder]^{k'}-[CON]^h-[Linker]^j-[CON]^{h'}-[CRBM]^{j'} (I) (a multispecific antigen binding molecule comprising a first antigen binding domain, and a second antigen binding domain, wherein the antigen binding domains comprise covalently associated binding polypeptides (a compound comprising formula (I): [Protein binder]^{k'}-[CON]^h-[Linker]^j-[CON]^{h'}-[CRBM]^{j'} (I)); paragraphs [0004], [0040]), wherein: the Protein binder is a molecule that binds to an extracellular protein (wherein D1 binds to an extracellular, optionally soluble antigen (the Protein binder is a molecule that binds to an extracellular protein); Figure 1, paragraphs [0004], [0008]); the CRBM is a cellular receptor binding moiety that binds to at least one receptor on the surface (D2 binds to an internalizing antigen on the surface of a cell (the CRBM is a cellular receptor binding moiety that binds to at least one receptor on the surface); Figure 1B, paragraphs [0004], [0008], [0059]) of a degrading cell in a subject, whereby binding of (I) leads to endocytosis and degradation of the extracellular protein (of a degrading cell in a subject, whereby binding of (I) leads to endocytosis and degradation of the extracellular antigen (extracellular protein); paragraphs [0003], [0059]); a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound (pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound; paragraph [0084]); and a method of treating, ameliorating, and/or preventing a disease or disorder in a subject, the method comprising administering a therapeutically effective amount of at least one compound (a method of treating, ameliorating, and/or preventing sepsis (a disease or disorder) in a subject, the method comprising administering a therapeutically effective amount of at least one compound paragraphs [0085], [0118]).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Regeneron reference, unity of invention is lacking.

-Continued From Box IV (iii)-

Groups I+, Claims 1-40, a compound encompassing Formula I, wherein the protein binder encompasses a moiety that binds to CD40L, as in claim 26, k' is 1, h, i, and h' are each 0; j' is 1, the CRBM encompasses folic acid (compound structure), and Addison's Disease (disease or disorder)

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Supplemental Box

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-Continued From Box V. 2: Citations and Explanations-

wide range of therapeutic agents; page 3, first paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Nalawansha, in order to have provided for wherein the CRBM is a folic acid folate receptor binder, as previously disclosed by Nalawansha in a separate embodiment (page 3, first paragraph), to adjust the structure of the conjugate to improve the properties of the conjugate in conducting targeted endocytosis of the protein of interest POI via lysosomal degradation (Nalawansha; page 3, figure 1). Further, provided that in both embodiments Nalawansha discloses the use of the conjugates of the ligands targeting cell surface receptors to enhance the transport of the agents or compounds across the membrane of living cells through the receptor-mediated endocytosis (Nalawansha; abstract; page 3, first paragraph; page 3, figure 1; page 5, figure 2A) (Wedeking; paragraphs [0008], [0061]), the modification to Nalawansha's compound, of providing for wherein the CRBM is a folic acid folate receptor binder, would provide the benefit of adjusting the structure of the conjugate to improve the properties of the conjugate in conducting targeted endocytosis of the protein of interest POI via lysosomal degradation (Nalawansha; page 3, figure 1).

As per claim 18, Nalawansha and Wedeking, in combination, disclose the compound of claim 1, and Nalawansha further discloses wherein the CRBM is: a folic acid folate receptor binder (folate receptor can be used to selectively deliver a wide range of therapeutic agents; page 3, first paragraph). Nalawansha does not disclose a folic acid folate receptor binder comprising folic acid. However, Wedeking discloses the folic acid folate receptor binder (the composition comprises macrocyclic and non-macrocyclic ligands selectively coupled to folate-receptor binding ligands; paragraph [0051]) comprising folic acid (in conjugate 36 shown in figure 14A, the folic acid residue shown in paragraph [0089], is linked directly to two chelating ligands 17b having conjugable amino function and shown in protected form in figure 8; figures 8, 14A; paragraphs [0074], [0089]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Nalawansha, in order to have provided for the folic acid folate receptor binder comprising folic acid, as previously disclosed by Wedeking (Wedeking; figures 8, 14A; paragraphs [0051], [0074], [0089]), to adjust the structure of the conjugate to improve the properties of the conjugate in conducting targeted endocytosis of the protein of interest POI via lysosomal degradation (Nalawansha; page 3, figure 1).

Claim 16 lacks an inventive step under PCT Article 33(3) as being obvious over Nalawansha in view of Wedeking, and further in view of the publication entitled "Asialoglycoprotein receptor mediated hepatocyte targeting — Strategies and applications" by D'Souza, et al. (hereinafter "D'Souza").

AAs per claim 16, Nalawansha and Wedeking, in combination, disclose the compound of claim 1, and Nalawansha further discloses the degrading cell (as shown in figure 1, the cell surface receptor binding ligand moiety binds G-protein coupled receptor GPCR on the surface of the cell that internalizes the complex with the attached protein of interest POI via endocytosis for lysosomal degradation, i.e., where the cell is the extracellular protein degrading cell; page 3, figure 1). Nalawansha does not disclose wherein the degrading cell comprises a hepatocyte. However, D'Souza discloses wherein the degrading cell comprises a hepatocyte (hepatocytes is an attractive target for asialoglycoprotein receptor-mediated drug delivery of drug-ligand conjugates with minimum-concerns of toxicity, which facilitates internalization by endocytosis and is useful for therapy of hepatic afflictions; abstract). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Nalawansha, in order to have provided for wherein the degrading cell comprises a hepatocyte, as previously disclosed by D'Souza (D'Souza; abstract), to provide additional information on the type of the cells that would be useful in the endocytosis-based protein degradation methodology targeting inflammation (Nalawansha; abstract; page 3, figure 1; page 5, figure 2A). Further, provided that Nalawansha and D'Souza both disclose potential therapeutic applications of the conjugates targeting cellular receptors for delivery of compounds (Nalawansha; abstract; page 3, figure 1; page 5, figure 2A) (D'Souza; abstract), the modification to Nalawansha's compound, of providing for wherein the degrading cell comprises a hepatocyte, would provide the benefit of providing additional information on the type of the cells that would be useful in the endocytosis-based protein degradation methodology targeting inflammation (Nalawansha; abstract; page 3, figure 1; page 5, figure 2A).

Claims 31-35 and 38-40 lack an inventive step under PCT Article 33(3) as being obvious over Nalawansha in view of Wedeking, and further in view of US 2004/0009907 A1 to Alsobrook II, et al. (hereinafter "Alsobrook").

As per claim 31, Nalawansha and Wedeking, in combination, disclose the compound of claim 1. Nalawansha does not disclose pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound. However, Alsobrook discloses pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound (active compound can be incorporated with excipients and used, pharmaceutical compositions include therapeutically-effective amounts of a therapeutic and a pharmaceutically-acceptable carrier; paragraphs [0008], [1719]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Nalawansha, in order to have provided for pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound, as previously disclosed by Alsobrook (Alsobrook; paragraphs [0008], [1719]), to provide the conjugates targeting cancer and inflammation (Nalawansha; abstract) in the pharmaceutically acceptable form to improve the effectiveness of the conjugates. Further, provided that Nalawansha and Alsobrook both disclose the use of the conjugates targeting host cell receptors to facilitate transport across the cell membrane (Nalawansha; abstract; page 3, figure 1; page 5, figure 2A) (Alsobrook; paragraph [1611]) for endocytosis (Nalawansha; abstract; page 3, figure 1; page 5, figure 2A) (Alsobrook; paragraphs [0115], [0459]) targeting inflammation (Nalawansha; abstract) (Alsobrook; paragraphs [1825], [1852], [2027]), the modification to Nalawansha's compound, of providing for pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound, would provide the benefit of providing the conjugates targeting cancer and inflammation (Nalawansha; abstract) in the pharmaceutically acceptable form to improve the effectiveness of the conjugates.

-Continued Within the Next Supplemental Box-

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Supplemental Box

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As per claim 32, Nalawansha, Wedeking and Alsobrook, in combination, disclose the pharmaceutical composition of claim 31. Nalawansha does not disclose comprising another therapeutically active agent that treats a disease or disorder. However, Alsobrook discloses comprising another therapeutically active agent (supplementary active compounds can also be incorporated into the compositions; paragraph [1715]) that treats a disease or disorder (nucleic acids and proteins are useful in therapeutic applications in diseases, i.e., for treatment of the diseases, when administered to a subject in need thereof; paragraph [0063]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the pharmaceutical composition, as previously disclosed by Nalawansha, in order to have provided for comprising another therapeutically active agent that treats a disease or disorder, as previously disclosed by Alsobrook (Alsobrook; paragraphs [0063], [1715]), to provide additional details on application of the conjugate in targeting inflammation and related conditions (Nalawansha; abstract).

As per claim 33, Nalawansha and Wedeking, in combination, disclose the compound of claim 1. Nalawansha does not disclose a method of treating a disease or disorder in a subject, the method comprising administering a therapeutically effective amount of at least one compound. However, Alsobrook discloses the method of treating a disease or disorder in a subject (nucleic acids and proteins are useful in therapeutic applications in diseases, i.e., for treatment of the diseases, when administered to a subject in need thereof; paragraph [0063]), the method comprising administering a therapeutically effective amount of at least one compound (nucleic acids and proteins are useful in therapeutic applications in diseases, i.e., for treatment of the diseases, when administered to a subject in need thereof, pharmaceutical compositions include therapeutically-effective amounts of a therapeutic; paragraphs [0008], [0063]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Nalawansha, in order to have provided for the method of treating a disease or disorder in a subject, the method comprising administering a therapeutically effective amount of at least one compound, as previously disclosed by Alsobrook (Alsobrook; paragraphs [0008], [0063]), to provide additional details on application of the conjugate in targeting inflammation and related conditions (Nalawansha; abstract).

As per claim 34, Nalawansha, Wedeking and Alsobrook, in combination, disclose the method of claim 33. Nalawansha does not disclose wherein the disease or disorder comprises an autoimmune disease. However, Alsobrook discloses wherein the disease or disorder comprises an autoimmune disease (Nramp1 regulates macrophage activation in infectious and autoimmune diseases, and further, gene CG57670-01 is expressed at low levels in the adrenal gland, and its activation increases oxidative metabolism in this tissue in a treatment for Addison's disease, where Addison's disease is the autoimmune disease, as disclosed in claim 35 of the instant application; paragraphs [0274], [2332]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Nalawansha, in order to have provided for wherein the disease or disorder comprises an autoimmune disease, as previously disclosed by Alsobrook (Alsobrook; paragraphs [0274], [2332]), to provide additional details on application of the conjugate in targeting inflammation and related conditions (Nalawansha; abstract).

As per claim 35, Nalawansha, Wedeking and Alsobrook, in combination, disclose the method of claim 34. Nalawansha does not disclose wherein the autoimmune disease comprises Addison's Disease. However, Alsobrook discloses wherein the autoimmune disease comprises Addison's Disease (gene CG57670-01 is expressed at low levels in the adrenal gland, and its activation increases oxidative metabolism in this tissue in a treatment for Addison's disease, where Addison's disease is the autoimmune disease, as disclosed in claim 35 of the instant application; paragraphs [0274], [2332]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Nalawansha, in order to have provided for wherein the autoimmune disease comprises Addison's Disease, as previously disclosed by Alsobrook (Alsobrook; paragraphs [0274], [2332]), to provide additional details on application of the conjugate in targeting inflammation and related conditions (Nalawansha; abstract).

As per claim 38, Nalawansha, Wedeking and Alsobrook, in combination, disclose the method of claim 33. Nalawansha does not disclose wherein the subject is further administered at least one additional therapeutic agent that treats the disease or disorder. However, Alsobrook discloses wherein the subject is further administered at least one additional therapeutic agent (supplementary active compounds can also be incorporated into the compositions; paragraph [1715]) that treats the disease or disorder (nucleic acids and proteins are useful in therapeutic applications in diseases, i.e., for treatment of the diseases, when administered to a subject in need thereof; paragraph [0063]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Nalawansha, in order to have provided for wherein the subject is further administered at least one additional therapeutic agent that treats the disease or disorder, as previously disclosed by Alsobrook (Alsobrook; paragraphs [0063], [1715]), to provide additional details on application of the conjugate in targeting inflammation and related conditions (Nalawansha; abstract).

As per claim 39, Nalawansha, Wedeking and Alsobrook, in combination, disclose the method of claim 33. Nalawansha does not disclose wherein the subject is a mammal. However, Alsobrook discloses wherein the subject is a mammal (the subject is a human subject; paragraph [0019]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Nalawansha, in order to have provided for wherein the subject is a mammal, as previously disclosed by Alsobrook (Alsobrook; paragraphs [0019]), to provide additional details on application of the conjugate in targeting inflammation and related conditions (Nalawansha; abstract).

As per claim 40, Nalawansha, Wedeking and Alsobrook, in combination, disclose the method of claim 33. Nalawansha does not disclose wherein the subject is a human. However, Alsobrook discloses wherein the subject is a human (the subject is a human subject; paragraph [0019]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Nalawansha, in order to have provided for wherein the subject is a human, as previously disclosed by Alsobrook (Alsobrook; paragraphs [0019]), to provide additional details on application of the conjugate in targeting inflammation and related conditions (Nalawansha; abstract).

-***-Continued Within the Next Supplemental Box-***-

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<div data-bbox="196 153 1385 210">Supplemental Box</div> <div data-bbox="196 210 1385 283"><p>In case the space in any of the preceding boxes is not sufficient. Continuation of:</p></div> <div data-bbox="196 283 1385 325"><p>---Continued from previous Supplemental Box---</p></div> <div data-bbox="196 325 1385 367"><p>Claim 26 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed matter.</p></div> <div data-bbox="196 367 1385 472"><p>Nalawansha discloses the Protein binder (as shown in figure 1, the extracellular protein of interest POI recruiting ligand moiety binds to the extracellular protein of interest POI; page 3, figure 1). However, Nalawansha does not disclose wherein the Protein binder binds to CD40L and comprises the moiety, as shown, where the stereo-chemical configuration of the cyclohexylglycine moiety is as shown, wherein the compound is conjugated to another compound through the pyrrolidine or cyclohexyl links, as shown.</p></div> <div data-bbox="196 472 1385 640"><p>US 2007/0249682 A1 to Zheng, et al. (hereinafter "Zheng") discloses wherein the Protein binder binds to CD40L (the compounds are CD40:CD154 binding compounds, CD154 is also known as CD40L, gp39, T-BAM, 5c8 antigen, CD40CR and TRAP; abstract; paragraph [0002]) and comprises the moiety, as shown (compound of formula 6, where the compound is derived from S-amines; paragraph [0048]), where the stereo-chemical configuration of the cyclohexylglycine moiety is as shown (the compound is derived from S-amines, the stereo-chemical configuration of the cyclohexylglycine moiety is as shown, and further, the stereo-chemical configuration of the cyclohexylglycine precursor 424 in column 3, line 2 in table II on page 14 is as shown; paragraphs [0048], [0095]). However, Zheng does not disclose wherein the compound is conjugated to another compound through the pyrrolidine or cyclohexyl links, as shown.</p></div> <div data-bbox="196 640 1385 808"><p>US 2016/0362450 A1 (Cara Therapeutics, Inc.) (hereinafter "Cara") discloses wherein the compound is conjugated to another compound through the pyrrolidine link (compounds were synthesized using Solid phase peptide chemistry, as shown in figure 2, the second compound is attached to the solid phase shown in dark circle, i.e., as a conjugate, through pyrrolidine link; figure 2; paragraph [0237]). However, Cara does not disclose wherein the Protein binder binds to CD40L and comprises the moiety, as shown, where the stereo-chemical configuration of the cyclohexylglycine moiety is as shown. Further, using the embodiment of Cara to modify the disclosure of Zheng can not be done without the benefit of impermissible hindsight.</p></div> <div data-bbox="196 808 1385 1123"><p>Nalawansha, Zheng, and Cara, alone or in combination, do not provide any motivation for providing for wherein the Protein binder binds to CD40L and comprises the moiety, as shown, where the stereo-chemical configuration of the cyclohexylglycine moiety is as shown, wherein the compound is conjugated to another compound through the pyrrolidine or cyclohexyl links, as shown, and though Zheng discloses wherein the Protein binder binds to CD40L and comprises the moiety, as shown, where the stereo-chemical configuration of the cyclohexylglycine moiety is as shown, Zheng does not disclose wherein the compound is conjugated to another compound through the pyrrolidine or cyclohexyl links, as shown. Cara discloses wherein the compound is conjugated to another compound through the pyrrolidine link. However, Cara does not disclose wherein the Protein binder binds to CD40L and comprises the moiety, as shown, where the stereo-chemical configuration of the cyclohexylglycine moiety is as shown. A combination of the references would not work because in order to meet the claim limitations, one would have to modify the compound disclosed by Nalawansha so that the compound would comprise the moiety, as shown, wherein the compound is conjugated to another compound through the pyrrolidine or cyclohexyl links, as shown. Additionally, Nalawansha does not express a desire to modify the compounds to include the limitations of the applicants. It would not be obvious to blend the compounds of the records of reference and would be impermissible hindsight in order to invent the applicant's compounds.</p></div> <div data-bbox="196 1123 1385 1165"><p>-----</p></div> <div data-bbox="196 1165 1385 1228"><p>Claims 1, 5-6, 16-18, 26, 31-35 and 38-40 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.</p></div>	

EXHIBIT 15



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/161,712	01/30/2023	David Spiegel	047162-7239US3(01833)	9168
78905	7590	09/11/2023	EXAMINER	
Saul Ewing LLP (Philadelphia) Attn: Patent Docket Clerk Centre Square West 1500 Market Street, 38th Floor Philadelphia, PA 19102-2186			LEE, JIA-HAI	
			ART UNIT	PAPER NUMBER
			1658	
			NOTIFICATION DATE	DELIVERY MODE
			09/11/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@saull.com

Office Action Summary

18/161,712

Applicant(s)

Spiegel et al.

Examiner

JIA-HAI LEE

Art Unit

1658

AIA (FITF) Status

Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 7/31/2023.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2a) ☐ This action is **FINAL**.

2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-2,4-8,10-18,20-24 and 26-28 is/are pending in the application.

5a) Of the above claim(s) 2,5,7-8,12-14,16-17 and 26 is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☒ Claim(s) 1,4,6,10-11,15,18,20-24 and 27-28 is/are rejected.

8) ☒ Claim(s) 6 is/are objected to.

9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☒ The drawing(s) filed on 1/30/2023 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date ____.

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: ____.

Paper No(s)/Mail Date ____.

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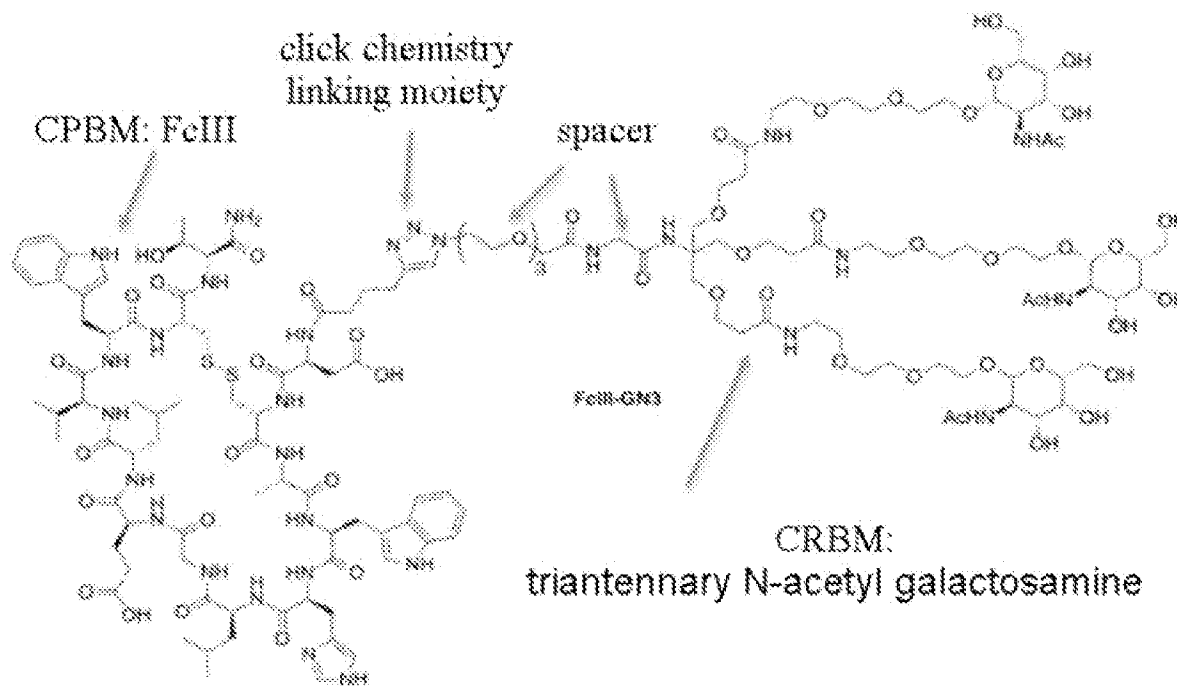
DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Election/Restrictions

Applicant's election without traverse of species election, FcIII, shown as follows in the reply filed on 7/31/2023 is acknowledged.



Claims 2, 5, 7-8, 12-14, 16-17, and 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/31/2023.

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Claim Status

Claims 1-2, 4-8, 10-18, 20-24, and 26-28 are pending.

Claims 3, 9, 19, and 25 are cancelled.

Claims 2, 5, 7-8, 12-14, 16-17, and 26 are withdrawn as being directed to a non-elected invention, the election having been made on 7/31/2023.

Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 have been examined.

Priority

This application is a CON of 17/695,645 filed on 03/15/2022

17/695,645 is a CIP of 17/046,221 filed on 10/08/2020

17/046,221 is a 371 of PCT/US2019/026260 filed on 04/08/2019

Information Disclosure Statement

There is NO IDS of Record.

Claim Objections

Claim 6 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 4.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 608.01(m).

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Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Claim 1 is unclear with respect to the relationship between CON_h , $Linker_{iL}$ and $CON_{h'}$ in the generic compound structure shown as follows.



- (i) Claim 1 describes each [CON] is optional (h and h' can be 0), but claim 1 also has the other limitation “h and h' are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15”, rendering the metes and bounds of the claims indefinite because the two limitations contradict to each other.
- (ii) Claim 1 describes the [LINKER] optionally itself contains one or more [CON] groups, rendering the metes and bounds of the claims indefinite because it is unclear which spacer region between CPBM and CRBM is CON_h , $Linker_{iL}$ and/or $CON_{h'}$. Neither the specification nor the claim 1 distinctly define a structure of CON or linker in the generic compound structure; thus, the compound structure of claim 1 is rejected as indefinite.
- (iii) Claim 1 states “[LINKER] is a chemical moiety having a valency of 1, 2, 3, ... or 15”. A

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convention knowledge recognizes “valency” as “the number of electrons that must be lost or gained by an atom to obtain a stable electron configuration” such as carbon atom with a valency of 4. Thus, it is unclear applicant’s definition of valency of [LINKER] leading to a valency of 1, 2, 3, ...or 15, rendering the metes and bounds of claim 1 indefinite.

(iv) Claim 1 is further unclear with respect to the phrase “[CRBM] is a Cellular Receptor Binding Moiety which binds to asialoglycoprotein receptors of hepatocytes or other cell receptors in the subject”. The metes and bounds of “or other cell receptors in the subject” is unclear because neither the specification nor the claim distinctly defines, not by examples, a structure of [CRMB] correlation to the capability of binding to a cell receptor.

Claims 4, 6, 10-11, 15, 18, 20-24, and 27-28 are rejected as either directly or indirectly depending on claim 1.

Improper Markush Grouping

Claims 1, 4, 6, 15, 18, 20, and 27-28 are rejected on the basis that it contains an improper Markush grouping of alternatives. See *In re Harnisch*, 631 F.2d 716, 721-22 (CCPA 1980) and *Ex parte Hozumi*, 3 USPQ2d 1059, 1060 (Bd. Pat. App. & Int. 1984). A Markush grouping is proper if the alternatives defined by the Markush group (i.e., alternatives from which a selection is to be made in the context of a combination or process, or alternative chemical compounds as a whole) share a “single structural similarity” and a common use. A Markush grouping meets these requirements in two situations. First, a Markush grouping is proper if the alternatives are all members of the same recognized physical or chemical class or the same art-recognized class, and are disclosed in the specification or known in the art to be functionally equivalent and have a common use. Second, where a Markush grouping describes alternative chemical compounds,

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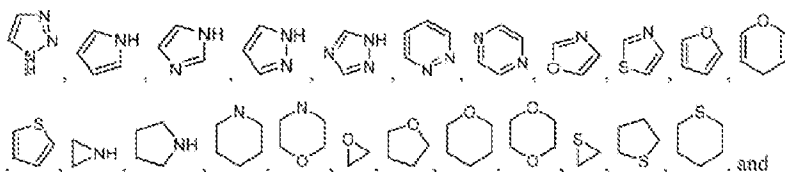
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whether by words or chemical formulas, and the alternatives do not belong to a recognized class as set forth above, the members of the Markush grouping may be considered to share a “single structural similarity” and common use where the alternatives share both a substantial structural feature and a common use that flows from the substantial structural feature. See MPEP § 706.03(y).

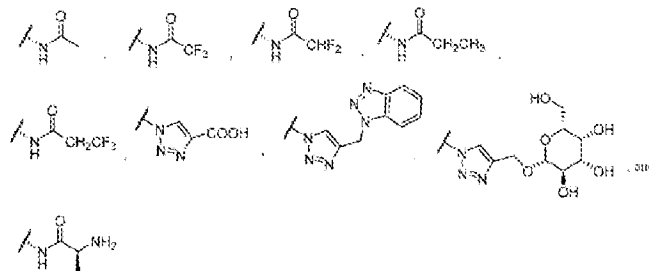
The Markush grouping of (i) Circulating Protein Binding Moiety (CPBM) in claims 1, 18, and 27 (ii) a laundry list of CYC structures in claims 4 and 6, (iii) R₂ moiety in claim 15, (iv) R₃ moiety in the compound structure in claim 20, and (v) a laundry list of bioactive agents in claim 28 are improper because the alternatives defined by the Markush grouping do not share both a single structural similarity and a common use for the following reasons:

(i) The CRBM moieties as claimed comprise linear peptides, cyclic peptides, and non-peptide compounds, but the CRBM moieties as claimed do not have a common structure or in the same art-recognized class. Furthermore, the claimed CRBM moieties bind to different target, (e.g., Low density lipoprotein receptor-related protein 1, alpha-2-macroglobulin receptor, Transferrin Receptor binding group, Macrophage Scavenger Receptor Binding Moiety) which are not functionally equivalent or have a common use to satisfy Markush grouping requirements.

(ii) a laundry list of CYC comprising 3, 5, and 6-member heterocyclic ring structures shown as follows do not share both a single structural similarity and a common use.



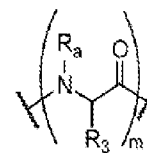
(iii) R₂ moieties listed in claim 15 do not share both a single structural similarity and a common use.



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(iv) R3 moieties in the compound structure shown as follows are side chains of different amino acids. Side chains of amino acids can be polar, hydrophobic, positive charge, negative charge, and a thiol group, but they do not share both a single structural similarity and a common use.



(v) a laundry list of bioactive agents in claim 28 do not share both a single structural similarity and a common use (treating a different type of cancer and/or targeting to a different cancer cell protein).

To overcome this rejection, Applicant may set forth each alternative (or grouping of patentably indistinct alternatives) within an improper Markush grouping in a series of independent or dependent claims and/or present convincing arguments that the group members recited in the alternative within a single claim in fact share a single structural similarity as well as a common use.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

(a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

Claims 1, 18, 20, 23, and 27-28 are rejected under 35 U.S.C. 102(a)(1) and (a)(2) as being anticipated by Spiegel et al. (US 2016/0082112 A1).

Claim 1 is drawn to a compound structure comprising a protein binding domain linked to

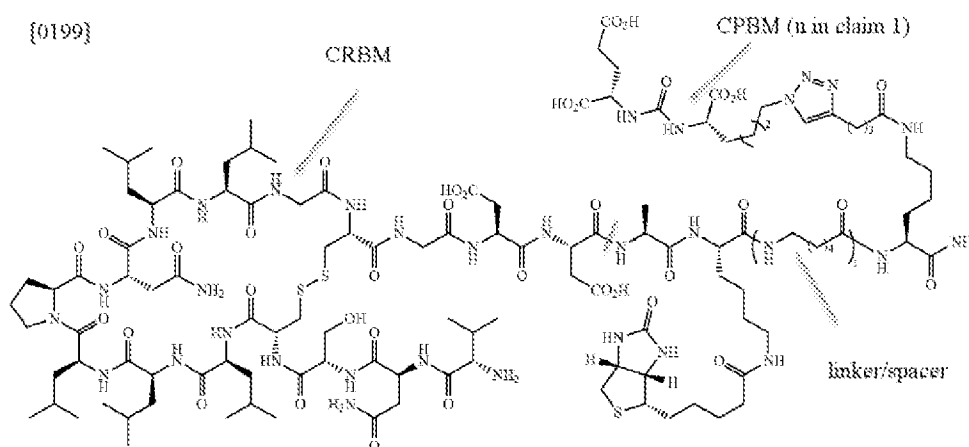
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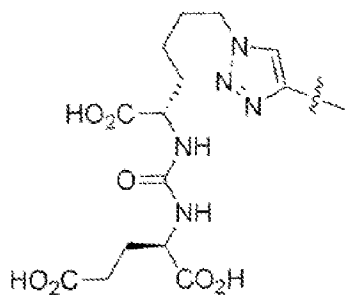
a cellular receptor binding domain via a spacer (CON and linker) shown as follows.



Spiegel et al. teach a bifunctional compounds comprising a soluble PSMA targeting motif (CPBM of claim 1(u)) and a Fc receptor binding domain of CRBM (e.g., CP33) of immune cells (Abstract). Spiegel et al. show the compound structure as follows [0199] comprising a CPBM as defined in claimed 1(u). Since applicant failed to distinctly define metes and bounds of CON and linker, the linker/spacer region comprising alanine, lysine, and triazole in the compound [0199] reads on the spacer comprising $\text{CON}_h\text{-Linker}_{iL}\text{-CON}_{h'}$ as claimed.



With respect to claim 18, Spiegel et al. show the CPBM as follows [0199].



With respect to claim 20, Spiegel et al. show the linking spacer comprising amino acid side chains of alanine and lysine [0199].

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With respect to claim 23, Spiegel et al. show the compound [0199] comprises a triazole moiety.

With respect to claim 27, Spiegel et al. teach a pharmaceutical composition comprising the compound in combination with a pharmaceutically effective amount of a carrier, additive or excipient [0138, claim 30].

With respect to claim 28, Spiegel et al. teach the composition further comprising one or more additional anti-cancer agents comprising docetaxel, doxorubicin; doxorubicin liposomal, fluorouracil, Interferon alfa-2a, Interferon alfa-2b, and other compounds as claimed [0121].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

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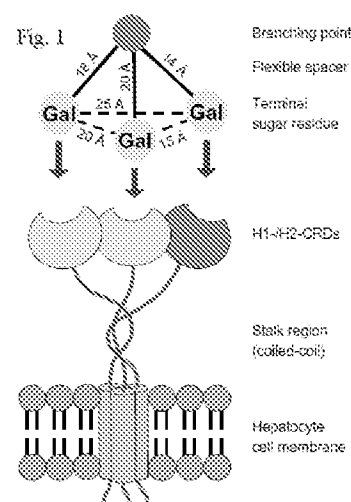
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 are rejected under 35 U.S.C. 103 as being unpatentable over Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.) in view of Guerrab et al. (Oncotarget. 2016; 7(45): 73618-73637) in view of Buckey et al. (Am J Clin Pathol 2008;129:245-251.) in view of Choe et al. (Materials. 2016, 9(12), 994) and evidenced by Zhu et al. (Angew. Chem. Int. Ed. 2023, 62, e202300694) and in view of Semple et al. (Journal of Polymer Science, Part A: Polymer Chemistry. 2016; 54: 2888–2895.)

Claim 1 is drawn to a compound structure as follows.



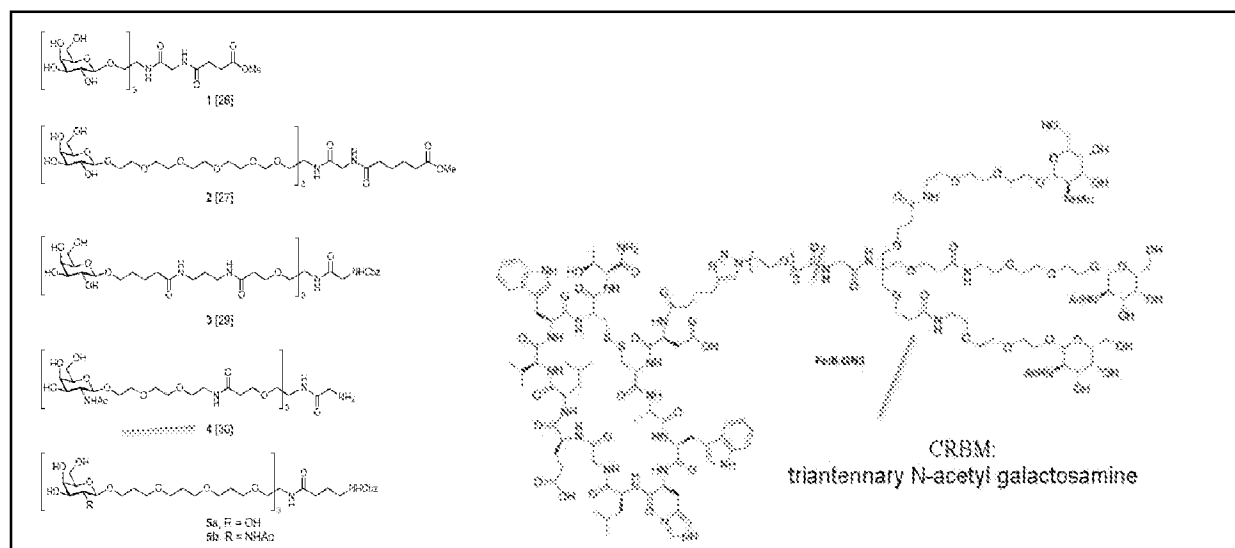
Khorev et al. teach “Trivalent, Gal/GalNAc-containing ligands designed for the asialoglycoprotein receptor” (Title). Khorev et al. teach triantennary ligands displayed a higher affinity than their mono- and diantennary counterparts. Khorev et al. further teach only the terminal residues are necessary for specific recognition, and that the binding process proceeds through a simultaneous interaction of 2–3 sugar residues with 2–3 binding sites of the heterooligomeric receptor of asialoglycoprotein receptor/ASGP-R (p5216, col 2, last para bridging to p5217, col 1, para 1) shown in figure 1 above. Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2), suggesting that the linking spacer



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comprising an alkyl chain substituted with oxygen (e.g., PEG) and/or amide bond do not



significantly affect the terminal galactose and N-acetylgalactosamine binding to

Asialoglycoprotein receptors of hepatocytes. Khorev's trivalent asialoglycoprotein receptor

targeting moiety compound 4 reads on the GN3 moiety of elected species as follows. Khorev et

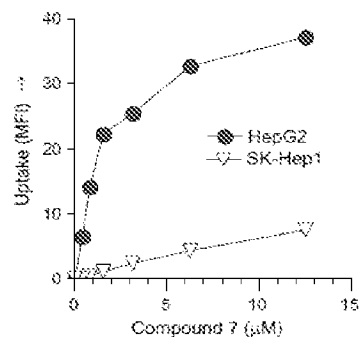
al. demonstrate a trivalent Gal/GalNAc targeting ligand is more

effective to internalize a conjugated compound into an

asialoglycoprotein receptor (ASGP-R) positive human

hepatocellular carcinoma HepG2 cell than an ASGP-R negative

SK-Hep1 cells as follows (p5222, Fig 5). Khorev et al. further



suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1).

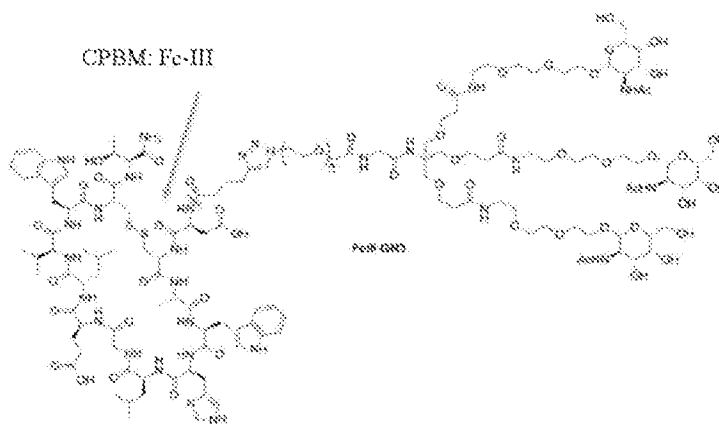
Khorev et al. do not teach a trivalent Gal/GalNAc targeting conjugate further linked to a circulating Protein Binding Moiety (CPBM).

Guerrab et al. teach administration of monoclonal antibody, cetuximab or panitumumab, and/or one tyrosine kinase inhibitor (EGFR-TKI; gefitinib or erlotinib) to treat cancer cells overexpression of epidermal growth factor receptor (EGFR) known in the art (Abstract).

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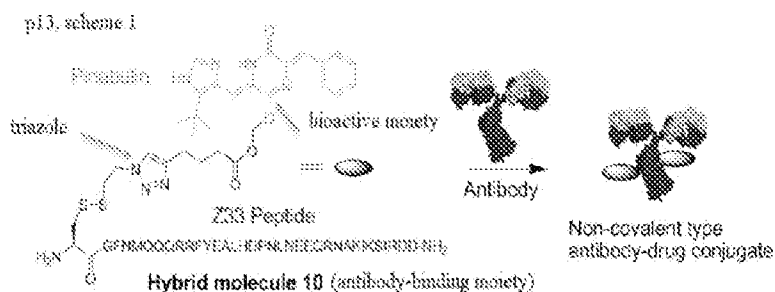
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Similarly, Buckley et al. teach overexpression of epidermal growth factor receptor (EGFR) has been observed in around 40% to 70% of conventional Hepatocellular carcinoma (HCC) in most studies. Buckley et al. further suggest administration of tyrosine kinase inhibitor (EGFR TKIs) anti-EGFR antibodies to treat EGFR expressing cancers (p245, col 2, para 2). Because (a) Hepatocellular carcinoma (HCC)



overexpresses epidermal growth factor receptor (EGFR) and (b) Guerrab et al. teach administration of monoclonal antibody, cetuximab or panitumumab, and/or one tyrosine kinase inhibitor (EGFR-TKI; gefitinib or erlotinib) to treat cancer cells overexpression of epidermal growth factor receptor (EGFR) as a common knowledge known in the art, one of ordinary skill in the art before the effective filing date of this invention would have found it obvious to administration Guerrab's monoclonal antibody of cetuximab or panitumumab to treat hepatocellular carcinoma or breast cancer overexpression of epidermal growth factor receptor (EGFR). Choe et al. teach Fc-binding ligand of immunoglobulin G (Title). Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards the Fc-

region of IgG was identified via phage display (p6, para 3), reading on the elected species of

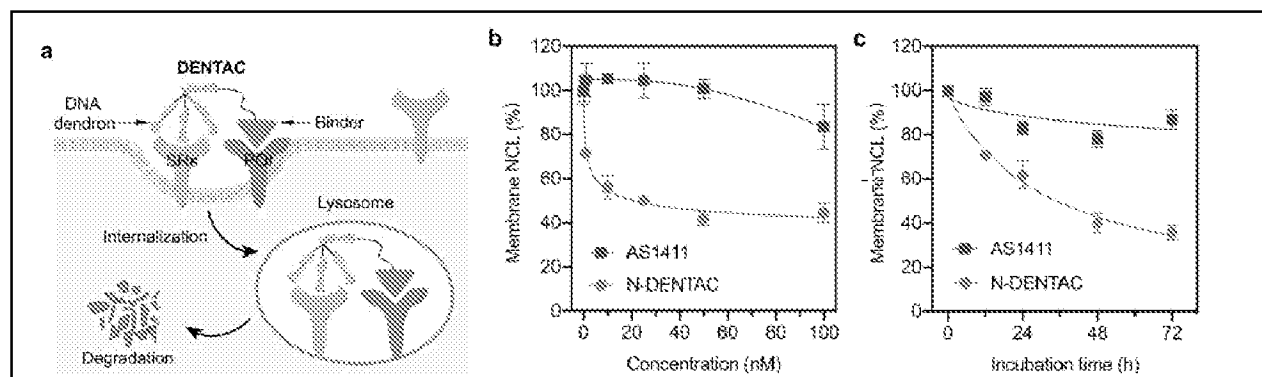


Fc-III shown above. Choe et al. show an antibody binding moiety is non-covalently bind to Fc region of an antibody and further suggest the use triazole as a linking moiety resulting from click

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chemistry reaction shown below (p13, scheme 1), suggesting that (bioactive agent)-Triazole-(Fc-binding peptide)--Antibody can form a complex in a single drug delivery system. Because (a) Khorevet et al. teach the use of trivalent asialoglycoprotein receptor targeting moiety for site-specific drug delivery to the human hepatocellular carcinoma (Abstract; p5220, col 2, 3. Biological evaluation), Choe et al. suggest the beneficial use of an Fc-binding peptide conjugate non-covalently binds to an antibody in a drug delivery system, and (c) Guerrab et al. in view of Buckley et al. suggest monoclonal antibody (cetuximab or panitumumab) able to treat EGFR expressing cancers (breast cancer and hepatocellular carcinoma), one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to select Khorevet's targeting moiety non-covalently linked to Guerrab's anti-cancer antibody (cetuximab or panitumumab) via Choe's high binding affinity of Fc-III to form a complex in a drug delivery system to treat specific hepatocellular carcinoma expressing EGFR and internalize antibody-bound EGFR via Khorev's trivalent Gal/GalNAc targeted asialoglycoprotein receptor for degradation as evidenced by Zhu et al. (p2, scheme 1a & p3, Fig 2b-2c) shown as follows.

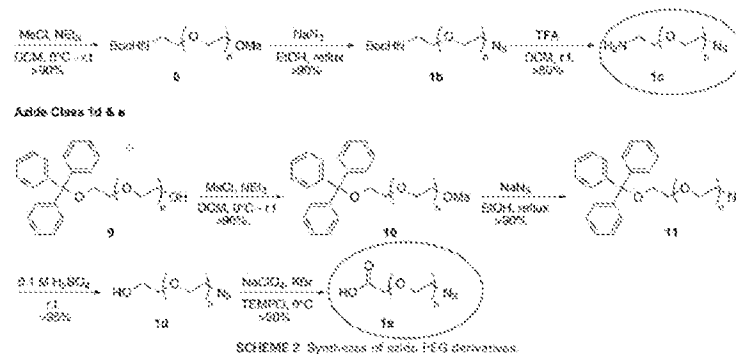


Khorev et al. in view of Guerrab et al. in view of Buckey et al. and in view of Choe et al. and evidenced by Zhu et al. do not explicitly teach a PEG linker functionalized with click chemistry reactive moiety to link Choe's Fc-binding peptide and Khorevet's targeting moiety together via a triazole moiety.

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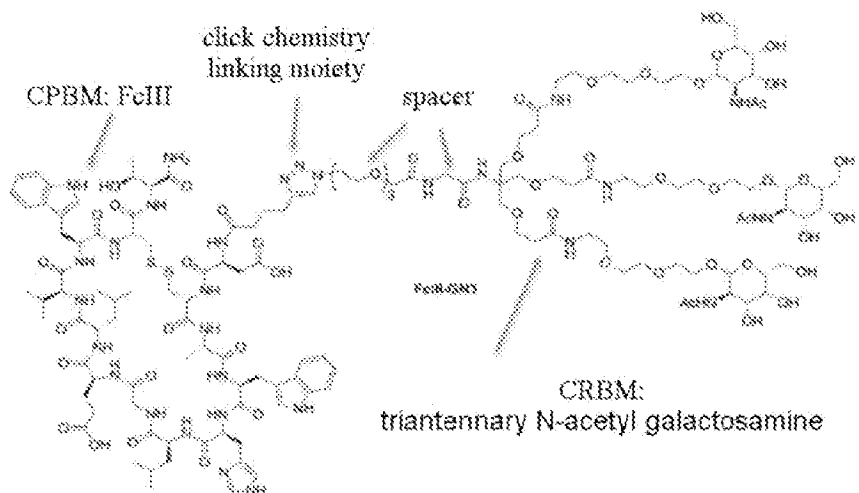
Semple et al. teach Poly(ethylene glycol) (PEG) derivatives have been applied in bioconjugation chemistry through the modification of peptides and proteins for drug delivery. Semple et al. suggest incorporation of PEG-containing moieties (PEGylation) into such systems generally improves pharmacological properties including increased water solubility, enhanced resistance to protein hydrolysis/degradation, improved bioavailability (circulation



half-life), and reduced antigenicity (p2888, col 1, Introduction). Semple et al. show synthesis of azido PEG derivative of compound 1c and 1e above (p2892, scheme 2). Semple et al. further show a click chemistry reaction for azido functionalized PEG derivative covalently linked to the counterpart click chemistry reactive moiety comprising to form triazole as follows (p2889, scheme 1). Khorev et al.

show a PEG repeating unit is 3 (e.g., compound 4 of Fig 2 shown above).

Because Semple et al. teach various advantages of using PEG derivatives in



bioconjugation chemistry for drug delivery (p2888, col 1, Introduction), one of ordinary skill in the art before the effective filing date of this invention would have found it beneficial use Semple's azido PEG derivative (compound 1e) as a bi-functional linker comprising a carboxylic group reacting to the amine group of Khorev's cell targeting moiety and an azido

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group reacting to acetylene functionalized Fc-III to form a triazole connecting moiety, reading on the elected species structure above.

One of ordinary skill in the art before the effective filing date of this invention would have found it obvious to combine Khorev's triantennary N-acetyl-galactosamine (CRMB) with Fc-binding peptide of CPBM taught by Guerrab et al. in view of Buckey et al. and Choe et al. because (a) Khorev et al. show trivalent Gal/GalNAc-containing ligands specifically binding to the asialoglycoprotein receptor of hepatocellular carcinoma (p5812, Fig 2; p5220, col 2, 3. Biological evaluation), (b) Guerrab et al. and Buckley et al. teach the common knowledge of (b)(i) overexpression of epidermal growth factor receptor (EGFR) has been observed in around 40% to 70% of conventional Hepatocellular carcinoma (HCC) taught by Buckley et al. (p245, col 2, para 2) and (b)(ii) the use of monoclonal antibodies (cetuximab or panitumumab) to treat EGFR positive cancer taught by Guerrab et al. (Abstract), and (c) Choe et al. teach the use of an Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) for non-covalently attached to an antibody in a drug delivery system (p13, scheme 1). The combination would have reasonable expectation of success because the references teach targeted therapy of a drug delivery system comprising a cellular targeting moiety, an antibody binding moiety, and an-anti-cancer drug (either an antibody or small a molecule compound).

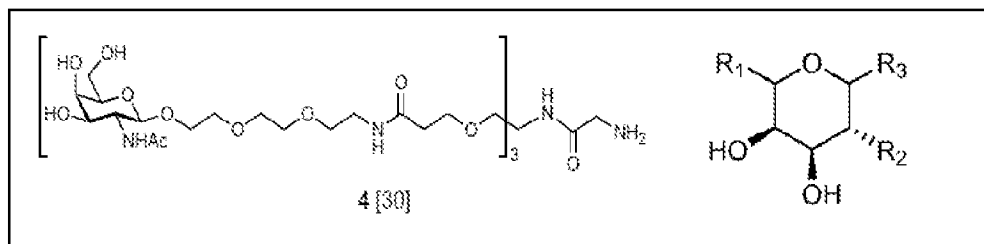
One of ordinary skill in the art before the effective filing date of this invention would have found it further obvious to combine Khorev et al. in view of Guerrab et al. in view of Buckey et al. and in view of Choe et al. evidenced by Zhu et al. with Semple's azido PEG spacer because (a) Khorev et al. in view of Guerrab et al. in view of Buckey et al. and in view of Choe et al. evidenced by Zhu et al. teach (triantennary ligands targeting moiety)-Triazole-(Fc-binding peptide)--Antibody forming a complex in a drug delivery system and (b) Semple et al. suggest

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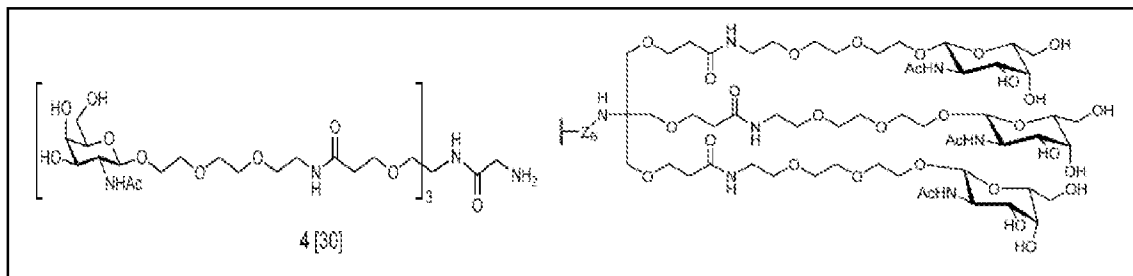
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beneficial incorporation of PEG-containing moieties (PEGylation) into such systems generally improves pharmacological properties including increased water solubility, enhanced resistance to protein hydrolysis/degradation, improved bioavailability (circulation half-life), and reduced antigenicity (p2888, col 1, Introduction) and show the use of azido PEG derivative for click chemistry to generate a conjugate via a connecting moiety of triazole (p2889, scheme 1). The combination would have reasonable expectation of success because both Choe et al. and Semple et al. teach the use of click chemistry to combine two moieties to form a conjugate via a click chemistry connecting moiety of triazole.

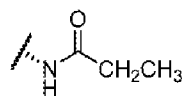
With respect to claims 4, 6, and 10, Khorev et al. show the CRBM as follows, reading on $R_1 = \text{CH}_2\text{OH}$ (K=1), $R_2 = \text{NH-CH}_2\text{-CH}_3$ (K=0), and $R_3 = \text{O-CH}_2\text{-CH}_2$ (K=0) shown as follows.



With respect to claim 11, Khorev et al. suggest CRBM of compound 4 shown below reading on $Z_B = \text{C(O)-(CH}_2\text{)-NH-}$.



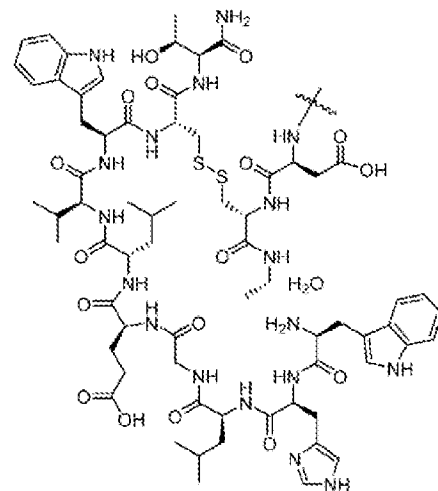
With respect to claim 15, Khorev's GalNAc targeting moiety reading on the structure of



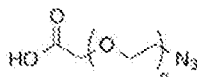
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With respect to claim 18, Choe et al. teach the use of an Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) for non-covalently attached to an antibody to generate a drug delivery system (p13, scheme 1), reading on the structure as follows.

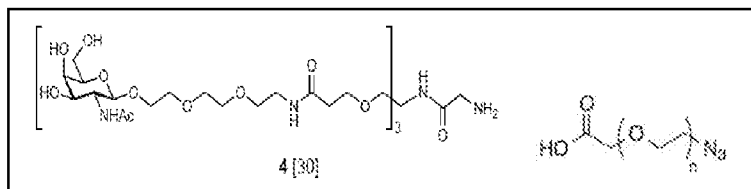


With respect to claims 20 and 22, Semple et al. show an azido PEG derivative linker

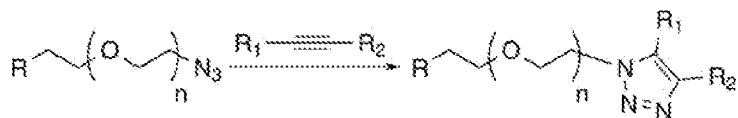


(p2892, scheme 2) comprising the structure as reading polyethylene glycol units between 1 and 100. Khorev et al. further show a PEG repeating unit is n=3 (e.g., compound 4 of Fig 2).

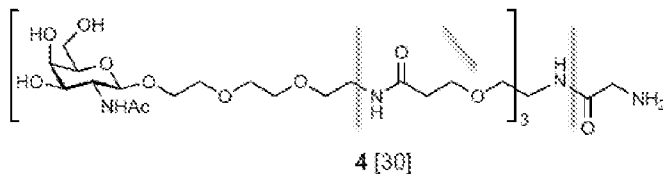
With respect to claim 21, Khorev's compound 4 comprises free amine group reacting to a carboxylic group of azido PEG derivative linker to form an amide bond (NH-CO), reading on Ram=H and na=0.



With respect to claim 23, Semple's azido PEG reacts to the other click chemistry reactive group to form a triazole group shown as follows, reading on



With respect to claim 24, Khorev's compound 4 comprises the [CON] shown as follows.



With respect to claim 27, Choe et al. teach Fc-binding peptide conjugate pre-mixed with antibody in a carrier solvent before injection (p12, Fig 9, legend).

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With respect to claim 28, Guerrab et al. suggest administration of a monoclonal antibody, cetuximab or panitumumab, and/or one tyrosine kinase inhibitor (EGFR-TKI; gefitinib or erlotinib) to treat cancer cells overexpression of epidermal growth factor receptor (Abstract), including hepatocellular carcinoma and breast cancer cells.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §

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2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

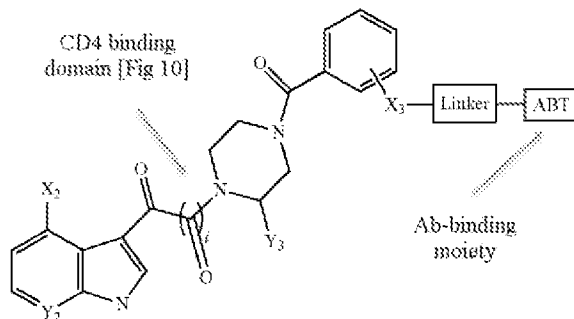
The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

1. Claims 1, 18, and 20-22 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 9,181,224 B2 (the ‘224 patent) in view of Choe et al. (Materials. 2016, 9(12), 994).

Claim 1 of the ‘224 patent disclosed a compound as follows.

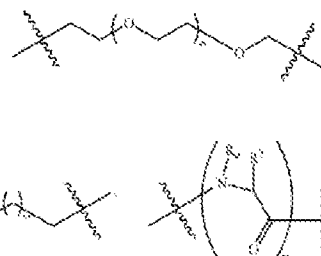
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Claim 1 of the '224 patent does not specify an antibody binding moiety as Fc-III (DCAWHLGELVWCT-NH2).

Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2, Figure 3a) with an unusual high binding affinity towards the Fc-region of antibody IgG was identified via phage display (p6, para 3), reading on the elected species of Fc-III. Because Choe et al. teach Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2, Figure 3a) with an unusual high binding affinity towards antibodies, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to use Choe's antibody binding domain of Fc-III to make the compound [Fc-III]-linker-[CD4 cellular receptor binding domain]. Thus, claim 1 of the '224 patent in view of Choe et al. is obvious to the instant claims 1 and 18.



Claim 6 of the '224 patent disclosed the linker as follows and R3 can be a side chain of alanine, satisfying the instant claims 20-22.

2. Claims 1, 18, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 6, and 20 of U.S. Patent No. 9,296,708 B2 (the '708 patent) in view of Choe et al. (Materials. 2016, 9(12), 994).

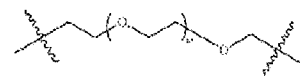
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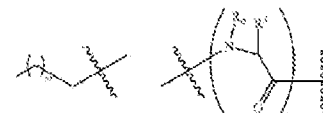
Claim 1 of the '708 patent disclosed a compound comprising an antibody binding moiety and a cell receptor binding moiety.

Claim 1 of the '708 patent does not specify an antibody binding moiety as Fc-III (DCAWHLGELVWCT-NH₂).

Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards the Fc-region of antibody IgG was identified via phage display (p6, para 3), reading on the elected species of Fc-III. Because Choe et al. teach Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards antibodies, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to modify antibody binding domain of the compound with Choe's antibody binding domain of Fc-III to make the compound [Fc-III]-Spacer-[cellular receptor binding domain]. Thus, claim 1 of the '708 patent in view of Choe et al. is obvious to the instant claims 1 and 18.



Claim 6 of the '224 patent disclosed the linker as follows and R₃ can be a side chain of alanine, satisfying the instant claims 20-22.



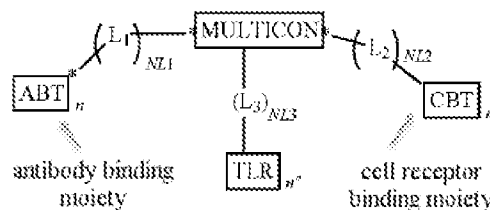
Claim 20 of the '224 patent disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

3. Claims 1, 18, 20-23, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-2, 18, 26, and 32 of U.S. Patent No. 9,556,167 B2 (the '167 patent) in view of Choe et al. (Materials. 2016, 9(12), 994).

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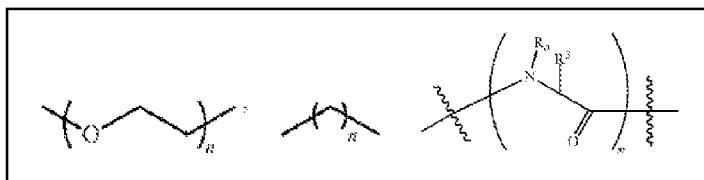
Claim 1 of the '167 patent disclosed a compound comprising an antibody binding moiety and a cell receptor binding moiety as follows.



Claim 1 of the '167 patent does not specify an antibody binding moiety as Fc-III (DCAWHLGELVWCT-NH2).

Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2, Figure 3a) with an unusual high binding affinity towards the Fc-region of antibody IgG was identified via phage display (p6, para 3), reading on the elected species of Fc-III. Because Choe et al. teach Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2, Figure 3a) with an unusual high binding affinity towards antibodies, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to modify the disclosed compound with Choe's antibody binding domain of Fc-III. Thus, claim 1 of the '167 patent in view of Choe et al. is obvious to the instant claims 1 and 18.

Claim 2 of the '167 patent disclosed the linker comprising PEG, alkyl, or amino acids (R3 can be a side chain of alanine) shown as follows, satisfying the instant claims 20-22.



Claim 18 of the '167 patent disclosed [CON] is a triazole group, satisfying the instant claim 23.

Claim 26 of the '167 patent disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

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Claim 32 of the '167 patent disclosed the pharmaceutical composition further comprising flutamide, bicalutamide, or nilutamide, satisfying the instant claim 28.

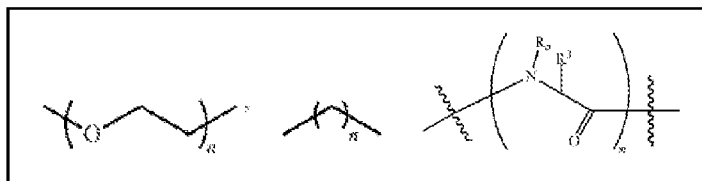
4. Claims 1, 18, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 21 of U.S. Patent No. 10,066,026 B2 (the '026 patent) in view of Choe et al. (Materials. 2016, 9(12), 994).

Claim 1 of the '026 patent disclosed a compound comprising an antibody binding moiety and a cell receptor binding moiety.

Claim 1 of the '026 patent does not specify an antibody binding moiety as Fc-III (DCAWHLGELVWCT-NH₂).

Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards the Fc-region of antibody IgG was identified via phage display (p6, para 3), reading on the elected species of Fc-III. Because Choe et al. teach Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards antibodies, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to modify the antibody-binding moiety of the compound with Choe's antibody binding domain of Fc-III to make the compound [Fc-III]-Spacer-[cellular receptor binding domain]. Thus, claim 1 of the '026 patent in view of Choe et al. is obvious to the instant claims 1 and 18.

Claim 1 of the '026 patent further disclosed a linker comprising PEG, alkyl, or amino acids (R₃ can be a side chain of alanine) shown as follows, satisfying the instant claims 20-22.



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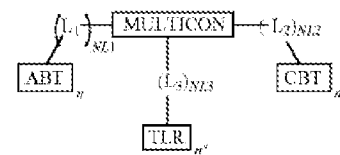
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Claim 1 of the '026 patent further disclosed [CON] is a triazole group, satisfying the instant claim 23.

Claim 21 of the '026 patent disclosed a pharmaceutical composition comprising the chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

5. Claims 1, 18, 20-22, and 27-28 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 14, 23-24 and 26 of U.S. Patent No. 10,016,412 B2 (the '412 patent) in view of Choe et al. (Materials. 2016, 9(12), 994).

Claim 1 of the '412 patent disclosed a compound comprising an antibody binding moiety (ABT) and cell receptor binding moiety (CBT) as follows.



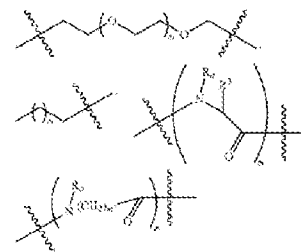
Claim 1 of the '412 patent does not specify an antibody binding moiety as Fc-III (DCAWHLGELVWCT-NH2).

Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2, Figure 3a) with an unusual high binding affinity towards the Fc-region of antibody IgG was identified via phage display (p6, para 3), reading on the elected species of Fc-III. Because Choe et al. teach Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2, Figure 3a) with an unusual high binding affinity towards antibodies, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to modify the antibody-binding moiety of the compound with Choe's antibody binding domain of Fc-III to make the compound [Fc-III]-Spacer-[cellular receptor binding domain]. Thus, claim 1 of the '026 patent in view of Choe et al. is obvious to the instant claims 1 and 18.

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Claim 14 of the '412 patent disclosed the linker structure disclosed a linker comprising PEG, alkyl, or amino acids (R3 can be a side chain of alanine) shown as follows, satisfying the instant claims 20-22.



Claims 23-24 of the '412 patent disclosed a pharmaceutical composition comprising the chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Claim 26 of the '412 patent disclosed the pharmaceutical composition further comprising a therapeutic agent, satisfying the instant claim 28.

6. Claims 1, 18, 20-22, and 27-28 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 14, 23-24 and 26 of U.S. Patent No. 10,633,374 B2 (the '374 patent) in view of Choe et al. (Materials. 2016, 9(12), 994).

Claim 1 of the '374 patent disclosed a compound comprising [CPBM]-spacer-[CRBM].

Claim 1 of the '374 patent does not specify an antibody binding moiety as Fc-III (DCAWHLGELVWCT-NH2).

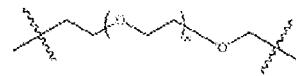
Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2, Figure 3a) with an unusual high binding affinity towards the Fc-region of antibody IgG was identified via phage display (p6, para 3), reading on the elected species of Fc-III. Because Choe et al. teach Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2, Figure 3a) with an unusual high binding affinity towards antibodies, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to modify antibody binding domain of the compound with Choe's antibody binding domain of Fc-III to make the compound [Fc-III]-

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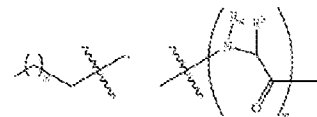
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Spacer-[cellular receptor binding domain]. Thus, claim 1 of the '374 patent in view of Choe et al. is obvious to the instant claims 1 and 18.

Claim 16 of the '374 patent disclosed the linker as follows and
 R3 can be a side chain of alanine, satisfying the instant claims 20-22.



Claim 31 of the '374 patent disclosed a pharmaceutical
 composition comprising a chimeric compound in combination with a pharmaceutically
 acceptable carrier, additive or excipient, satisfying the instant claim 27.



7. Claims 1, 18, 20-22, and 27-28 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 14, 23-24 and 26 of U.S. Patent No. 10,703,823 B2 (the '823 patent) in view of Choe et al. (Materials. 2016, 9(12), 994).

Claim 1 of the '823 patent disclosed a compound comprising [CPBM]-spacer-[CRBM].

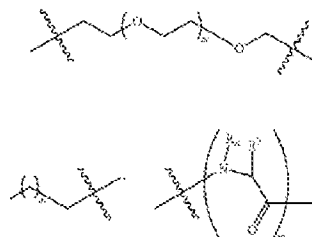
Claim 1 of the '823 patent does not specify an antibody binding moiety as Fc-III (DCAWHLGELVWCT-NH2).

Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2, Figure 3a) with an unusual high binding affinity towards the Fc-region of antibody IgG was identified via phage display (p6, para 3), reading on the elected species of Fc-III. Because Choe et al. teach Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2, Figure 3a) with an unusual high binding affinity towards antibodies, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to modify antibody binding domain of the compound with Choe's antibody binding domain of Fc-III to make the compound [Fc-III]-Spacer-[cellular receptor binding domain]. Thus, claim 1 of the '823 patent in view of Choe et al. is obvious to the instant claims 1 and 18.

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Claim 10 of the '823 patent disclosed the linker as follows
and R3 can be a side chain of alanine, satisfying the instant claims
20-22.



Claim 19 of the '823 patent disclosed a pharmaceutical
composition comprising the chimeric compound in combination with a pharmaceutically
acceptable carrier, additive or excipient, satisfying the instant claim 27.

8. Claims 1, 18, 20-22, and 27-28 are rejected on the ground of nonstatutory double
patenting as being unpatentable over claims 1, 14, 23-24 and 26 of U.S. Patent No. 10,912,836
B2 (the '836 patent).

Claim 1 of the '836 patent disclosed a compound comprising a cellular FcγRI receptor
binding moiety and a soluble PSMA targeting motif with a spacer, satisfying the instant claim 1.

Claim 1 of the '836 patent further disclosed the compound composition further
comprising a pharmaceutically acceptable salt, reading on excipient and satisfying the instant
claim 27.

9. Claims 1, 18, 20-23, and 27 are rejected on the ground of nonstatutory double patenting
as being unpatentable over claims 1, 10 and 16 of U.S. Patent No. 11,014,992 B2 (the '992
patent) in view of Choe et al. (Materials. 2016, 9(12), 994).

Claim 1 of the '992 patent disclosed a compound comprising [CPBM]-spacer-[CRBM].

Claim 1 of the '992 patent does not specify an antibody binding moiety as Fc-III (
DCAWHLGELVWCT-NH2).

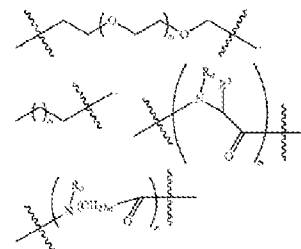
Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH2,

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Figure 3a) with an unusual high binding affinity towards the Fc-region of antibody IgG was identified via phage display (p6, para 3), reading on the elected species of Fc-III. Because Choe et al. teach Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards antibodies, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to modify antibody binding domain of the compound with Choe's antibody binding domain of Fc-III to make the compound [Fc-III]-Spacer-[cellular receptor binding domain]. Thus, claim 1 of the '992 patent in view of Choe et al. is obvious to the instant claims 1 and 18.

Claim 10 of the '992 patent disclosed the linker structure disclosed a linker comprising PEG, alkyl, or amino acids (R₃ can be a side chain of alanine) shown as follows, satisfying the instant claims 20-22.



Claim 10 of the '992 patent further disclosed [CON] is a triazole group, satisfying the instant claim 23.

Claim 16 of the '992 patent disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

10. Claims 1, 18, 20-23, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 10 and 16 of U.S. Patent No. 11,725,064 B2 (the '064 patent) in view of Choe et al. (Materials. 2016, 9(12), 994).

Claim 1 of the '064 patent disclosed a compound comprising [CPBM]-spacer-[CRBM].

Claim 1 of the '064 patent does not specify an antibody binding moiety as Fc-III (

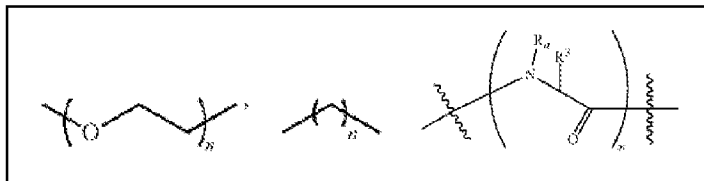
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DCAWHLGELVWCT-NH₂).

Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards the Fc-region of antibody IgG was identified via phage display (p6, para 3), reading on the elected species of Fc-III. Because Choe et al. teach Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards antibodies, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to modify antibody binding domain of the compound with Choe's antibody binding domain of Fc-III to make the compound [Fc-III]-Spacer-[cellular receptor binding domain]. Thus, claim 1 of the '992 patent in view of Choe et al. is obvious to the instant claims 1 and 18.

Claim 3 of the '992 patent disclosed the linker comprising PEG, alkyl, or amino acids (R₃ can be a side chain of alanine) shown as follows, satisfying the instant claims 20-22.



Claim 4 of the '992 patent disclosed [CON] is a triazole group, satisfying the instant claim 23.

Claim 26 of the '992 patent disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

11. Claims 1, 18, 20, 22-23, and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 20, and 66 of copending Application No. 16/634032 (the '032 application). Although the claims at issue are not identical, they are not

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patentably distinct from each other because the '032 application anticipates this instant application.

Claim 1 of the '032 application disclosed a compound comprising [CPBM]-spacer [CRBM].

Claim 64 of '032 application disclosed an antibody binding moiety as Fc-III (DCAWHLGELVWCT-NH2).

Thus, claim 1 in view of 64 of the '032 application is obvious to the instant claims 1 and 18.

Claim 20 of '032 application disclosed s linking moiety comprising triazole and PEG, satisfying the instant claims 20 and 22-23.

Claim 66 of '032 application disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

This is a provisional nonstatutory double patenting rejection.

12. Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 12, 33, and 37 of copending Application No. 17/046,192 (the '192 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '192 application anticipates this instant application.

Claim 1 of the '192 application disclosed a bi-functional compound as follows.

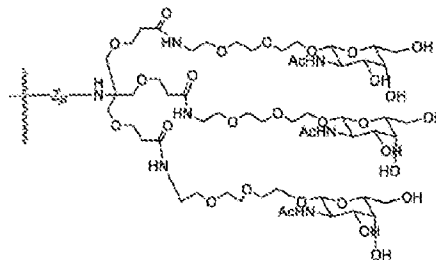


Claim 1 of the '192 application disclosed the CPBM moiety as the elected Fc-III.

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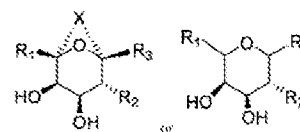
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Claim 12 of the '192 application disclosed the CRBM as the elected species shown as follows.



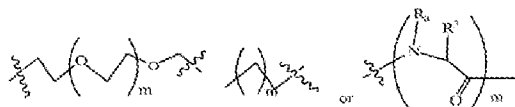
Claim 1 of the '192 application further disclosed the number for repeating units of each moiety reads on the claimed limitations. Thus, claims 1 and 12 of the '192 application anticipate this instant claim 1, 11, 18, and 27.

Claim 1 of the '192 application disclosed the CRBM comprises a sugar moiety as follows, satisfying the instant claims 4, 6, and 10.



Claim 12 of the '192 application disclosed the [ASGPRBM] group, satisfying the instant claims 11, 15, and 24.

Claim 1 of the '192 application further disclosed a linker PEG, alkyl, or amino acids (R3 can be a side chain of alanine) shown as follows, satisfying the instant claims 20-22.



Claim 1 of the '192 application disclosed a [CON] as a triazole, satisfying the instant claim 23.

Claim 33 of the '192 application disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Claim 37 of the '192 application disclosed the pharmaceutical composition comprising an bioactive agent, satisfying the instant claim 28.

This is a provisional nonstatutory double patenting rejection.

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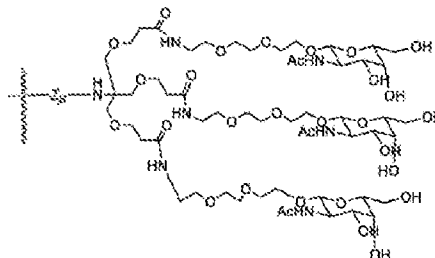
13. Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4, 6, 10, 12, 18, 24, 29-30, 32, and 37 of copending Application No. 17/046,221 (the '221 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '221 application anticipates this instant application.

Claim 1 of the '221 application disclosed a bi-functional compound as follows.



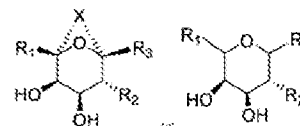
Claim 4 of the '221 application disclosed the CPBM moiety as the elected Fc-III.

Claim 12 of the '221 application disclosed the CRBM as the elected species shown as follows.



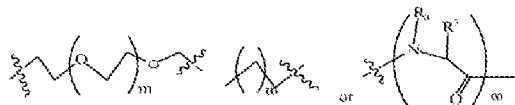
Claim 1 of the '221 application further disclosed the number for repeating units of each moiety reads on the claimed limitations. Thus, claims 1, 4, and 12 of the '221 application anticipate this instant claim 1, 11, 18, and 21.

Claims 4 and 11 of the '221 application disclosed CRBM comprising , satisfying the instant claims 4, 6, and 10.



Claim 18 of the '221 application disclosed R2 moiety, satisfying the instant claim 15

Claim 24 of the '221 application further disclosed a linker PEG, alkyl, or amino acids (R3 can be a side chain of alanine) shown as follows, satisfying the instant claims 20-22.



Claim 29 of the '221 application disclosed a [CON] as a triazole, satisfying the instant claim 23.

Claim 30 of the '221 application disclosed a [CON] structure, satisfying the instant claim

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24.

Claim 32 of the '221 application disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Claim 37 of the '221 application disclosed the pharmaceutical composition comprising an bioactive agent, satisfying the instant claim 28.

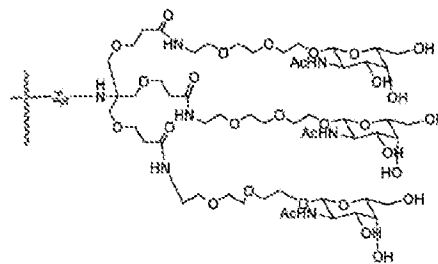
This is a provisional nonstatutory double patenting rejection.

14. Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 15-16, 19-20, 23, 27 and 30 of copending Application No. 17/654,990 (the '990 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '990 application anticipates this instant application.

Claims 1 and 13 of the '990 application disclosed a compound formula (III) above.

Claim 15 of the '990 application disclosed CRBM as asialoglycoprotein receptor binder.

Claim 20 of the '990 application disclosed CRBM structure as the elected species shown as follows.



Claim 27 of the '990 application disclosed AATM as the elected species of a cyclic peptide FcIII.

Claim 1 further defined the repeating units of CON and Linker satisfying the limitations as claimed. Thus, claims 1, 15, 20, and 27 anticipate this instant claim 1.

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Claim 16(j) of the '990 application disclosed an [ASGPRBM], satisfying the instant claims 4 and 6.

Claim 19 of the '990 application disclosed an [ASGPRBM], satisfying the instant claim 10.

Claim 20 of the '990 application disclosed CRBM structure as the elected species shown above, satisfying the instant claims 15 and 20.

Claim 27 of the '990 application disclosed AATM as the elected species of a cyclic peptide FcIII, satisfying the instant claim 18.

Claim 20 of the '990 application disclosed CRBM as asialoglycoprotein receptor binder with a spacer comprising PEG spacer and amide bonds (na=0), satisfying the instant claims 20-23.

Claim 23 of the '990 application disclosed various [CON] structures, satisfying the instant claim 24.

Claim 30 of the '990 application disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

This is a provisional nonstatutory double patenting rejection.

15. Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3, 5, 9-10, 14, 16, 18, 21-23, and 26-27 of copending Application No. 17/695,259 (the '259 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '259 application anticipates this instant application.

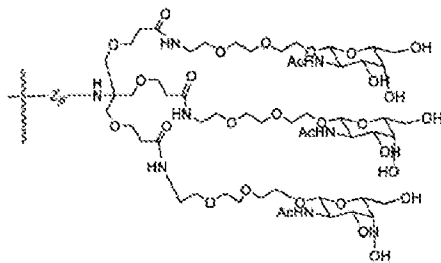
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Claim 1 of the '259 application disclosed a compound formula as follows.

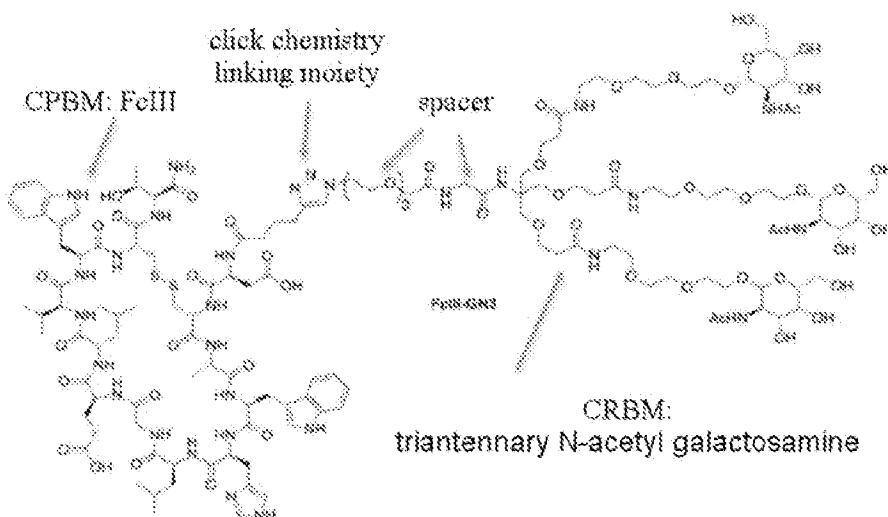


Claim 10 of the '259 application disclosed the [ASGPRBM] group a follows



Claims 3 and 16 of the '259 application disclosed IgGBM moiety as FcIII.

Claim 23 disclosed the elected compound structure of FcIII-GN3



Thus, claims 1, 3, 5, 9-10, 14, 16, 18, 21-22, and 23 (elected species) of the '259 application anticipate the instant claims 1, 4, 6, 10-11, 15, 18, and 20-24.

Claim 26 of the '259 application disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Claim 27 of the '259 application disclosed the pharmaceutical composition comprising an

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bioactive agent, satisfying the instant claim 28.

This is a provisional nonstatutory double patenting rejection.

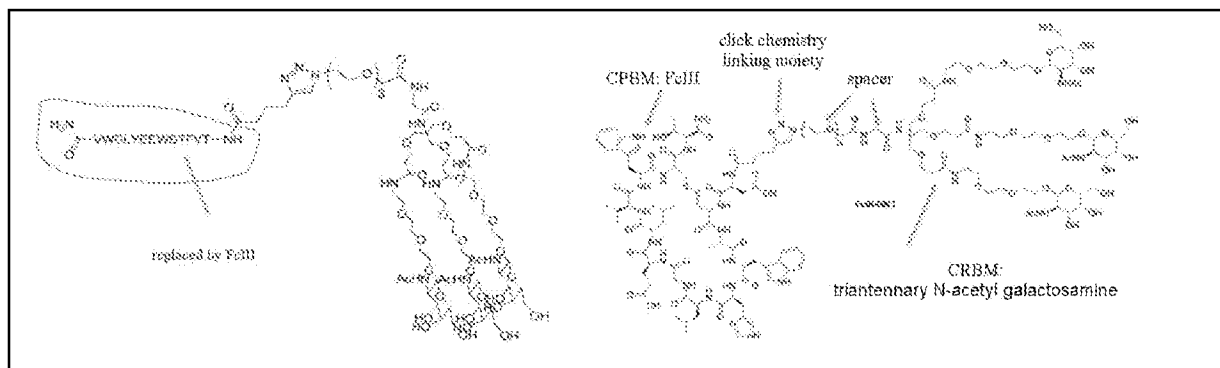
16. Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4, 6, 10-11, 15, 18, 20-24 and 28 of copending Application No. 17/695,645 (the '645 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '645 application is obvious to this instant application.

Claim 1 of the '645 application disclosed a compound as follows.



Claims 3 and 17 the '645 application disclosed CPBM is FcIII.

Claim 24 the '645 application disclosed a compound structure. When a simple substitution of the circled CPBM with FcIII, the FcIII-substituted compound reads on the elected species as follows.



Thus, claims 1, 3, 5, 7, 9-10, 14, 17, 19, 22-23 of the '645 application are obvious to the instant claims 1, 4, 6, 10-11, 15, 18, and 20-24.

Claim 26 of the '259 application disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or

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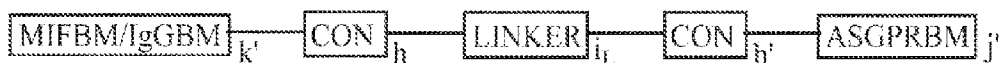
excipient, satisfying the instant claim 27.

Claim 27 of the '259 application disclosed the pharmaceutical composition comprising an bioactive agent, satisfying the instant claim 28.

This is a provisional nonstatutory double patenting rejection.

17. Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3, 9-10, 14, 16, 18, 21-23, and 26-27 of copending Application No. 18/161,633 (the '633 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '633 application anticipates this instant application.

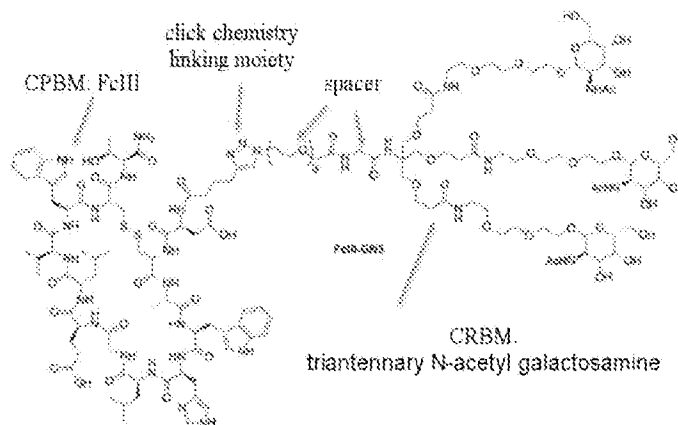
Claim 1 of the '633 application disclosed a bifunctional compound as follows.



Claims 3 and 16-17 of the '633 application disclosed IgGBM moiety as FcIII.

Claim 10 of the '633 application disclosed [ASGPRBM] structure.

Claim 26 of the '633 application disclosed the elected species of FcIII-linker-[ASGPRBM], FcIII-GN3, structure as follows. Thus, claims 1,3, 9-10, 14, 16-17, 19, 22-23, and 26 are obvious to the instant claims 1, 4, 6, 10-11, 15, 18, and 20-24.



Claim 28 of the '633 application disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

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This is a provisional nonstatutory double patenting rejection.

18. Claims 1, 18, 20-23, and 27-28 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 12-13, 23, and 26 of copending Application No. 18/206,937 (the '937 application) in view of Choe et al. (Materials. 2016, 9(12), 994).

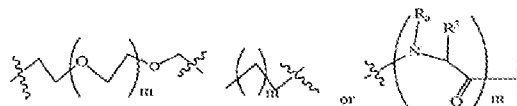
Claim 1 of the '937 application disclosed a compound comprising an antibody binding moiety and a cell receptor binding moiety.

Claim 1 of the '937 application does not specify an antibody binding moiety as Fc-III (DCAWHLGELVWCT-NH₂).

Choe et al. teach a 13-mer Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards the Fc-region of antibody IgG was identified via phage display (p6, para 3), reading on the elected species of Fc-III. Because Choe et al. teach Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards antibodies, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to modify antibody binding domain of the compound with Choe's antibody binding domain of Fc-III to make the compound [Fc-III]-Spacer-[cellular receptor binding domain]. Thus, claim 1 of the '937 application in view of Choe et al. is obvious to the instant claims 1 and 18.

Claim 12 of the '937 application disclosed a linker PEG, alkyl, or amino acids (R₃ can be a side chain of alanine) shown as follows,

satisfying the instant claims 20-22.



Claim 13 of the '937 application disclosed [CON] as a triazole, satisfying the instant

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claim 23.

Claim 23 of the '937 application disclosed a pharmaceutical composition comprising a chimeric compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Claim 26 of the '937 application disclosed the pharmaceutical composition comprising an bioactive agent, satisfying the instant claim 28.

This is a provisional nonstatutory double patenting rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JIA-HAI LEE whose telephone number is (571)270-1691. The examiner can normally be reached Mon-Fri from 9:00 AM to 6:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melissa Fisher can be reached on 571-270-7430. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit:

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<https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L./

Examiner, Art Unit 1658

04-September-2023

/ARADHANA SASAN/

Primary Examiner, Art Unit 1615

EXHIBIT 16

U.S. Patent Application No. 047162-7259033 (01855)
Attorney Docket No. 047162-7259033 (01855)
Response to non-final Office Action issued September 11, 2023

Remarks

Claims 1-2, 4-8, 10-18, 20-24, and 26-28 were pending, with claims 2, 5, 7-8, 12-14, 16-17, and 26 withdrawn from consideration. Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 were thus under consideration.

Claims 1, 16-18, 20-22, and 27 are amended. Claims 4-15, 23-24, and 28 are canceled.

Upon entry of this Response, claims 1, 18, 20-22, and 27 will be pending for consideration on the merits.

Amendments to the Claims

Claims 1, 16-18, 20-22, and 27 are amended to more particularly point out and distinctly claim the inventive subject matter and/or to perfect antecedent basis. Support for the amendments is found in the application and claims as originally filed.

Claims 4-15, 23-24, and 28 are canceled without prejudice or disclaimer. Applicant reserves the right to file the subject matter of any canceled claim(s) in any later filed continuation, continuation-in-part, and/or divisional application(s).

No new matter has been added by the amendments herein.

Objections to the Claims

Claim 6 was objected to as being a substantial duplicate of claim 4.

Applicant has canceled both claims 4 and 6, rendering this objection moot. Withdrawal of the objection is respectfully requested.

Response to Rejection under 35 U.S.C. § 112

Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 stand rejected under 35 U.S.C. § 112(b) as allegedly indefinite. This rejection is respectfully traversed.

The rejection of claims 4, 6, 10-15, 23-24, and 28 is moot in view of their cancelation.

The Action indicates that h and h' have contradictory definitions, the structure of [CON] is not defined, the valency of [LINKER] is unclear, and the term “or other cell receptors in the subject” is unclear.

As noted elsewhere herein, claim 1 is amended in part to specify that the values of h and h' are non-zero, to define specific structures for [CON] and [LINKER], and to delete the term “or

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 Attorney Docket No. 047162-7259033 (01855)
 Response to non-final Office Action issued September 11, 2023

other cell receptors in the subject.”

Accordingly, amended claim 1 and the claims dependent therefrom, comply with the requirements of 35 U.S.C. § 112(b).

Withdrawal of the rejection is respectfully requested.

Response to Rejection for Improper Markush Group

Claims 1, 4, 6, 15, 18, 20, and 27-28 are rejected as allegedly containing an improper Markush group. This rejection is respectfully traversed.

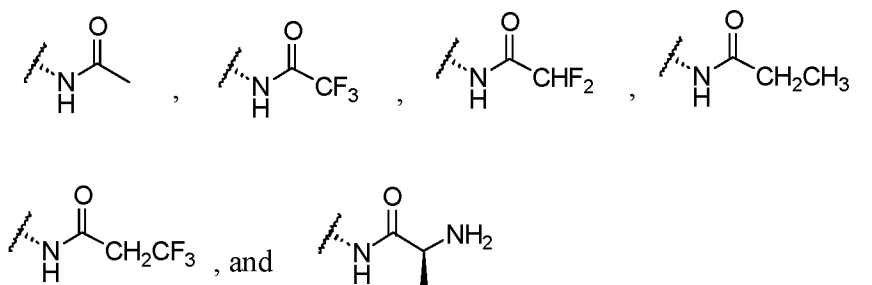
The rejection of claims 4, 6, 15, and 28 is moot in view of their cancelation.

The Office indicated that the CRBM moieties bound to different protein targets and allegedly are not functionally equivalent or have a common use to satisfy Markush grouping requirements.

Without conceding to the propriety of the rejection, and solely to advance prosecution, independent claims 1 and 27 are amended to recite, in part, that the CRBM is an IgG binding moiety. Thus, only so far as Markush grouping requirements are concerned, the claimed CRBM moieties are functionally equivalent and/or have a common use in *binding to IgG*.

With respect to the “laundry list” of CYC groups and R₃ moieties containing various amino acid sidechains, Applicant has deleted that subject matter from the claims.

With respect to the R₂ moieties not sharing a structural similarity and a common use, Applicant has, without conceding to the propriety of the rejection, amended the list of R₂ groups to recite:



The amended list of R₂ moieties are all amide derivatives and share a common use in being a part of an aminoglycan that binds to asialoglycoprotein receptor. Thus, the R₂ groups have both a common structural similarity and a common purpose. Applicant notes that to the extent any bright-line rule might be applied that focuses solely on the structural differences

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 Attorney Docket No. 047162-7239033 (01833)
 Response to non-final Office Action issued September 11, 2023

without consideration of other structural similarities, that approach would be incorrect. *See In re Harnisch*, 631 F.2d 716, 722 (CCPA 1980) (“[I]n determining the propriety of a Markush grouping the compounds must be considered as wholes and not broken down into elements or other components.”); *see also* MPEP § 2117 (IV). The common use of the claimed compounds is to bind one end of the compound to IgG and the other end to asialoglycoprotein receptor. Accordingly, the pending amended claims recite proper Markush groups.

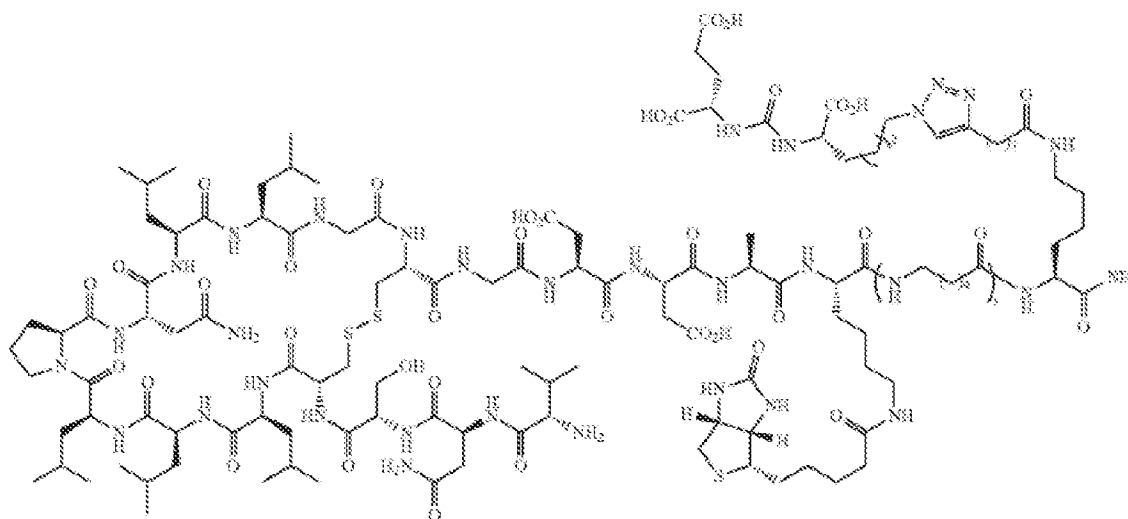
Withdrawal of the rejection is respectfully requested.

Response to Rejection under 35 U.S.C. § 102

Claims 1, 18, 20, 23, and 27-28 stand rejected under 35 U.S.C. § 102(a)(1) and (a)(2) as allegedly anticipated by US 2016/0082112 A1 (“Spiegel”). This rejection is respectfully traversed.

The rejection of claim 23 is moot in view of its cancelation.

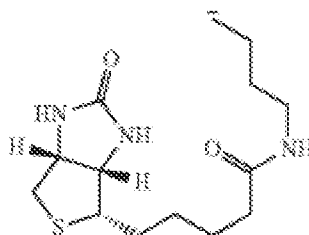
The Office alleges that the following compound described in paragraph [0199] of Spiegel renders the claims anticipated:



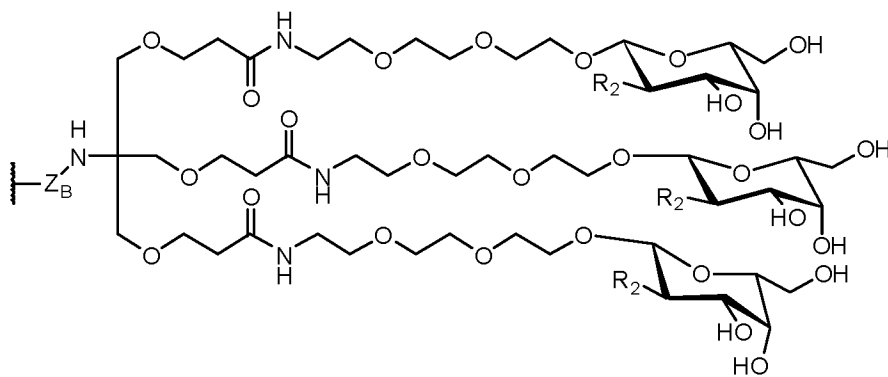
Applicant respectfully disagrees at least in view of the amendments to claims 1 and 27.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.

Amended claims 1 and 27 recite specific definitions for [CPBM], [CRBM], [CON], and [LINKER]. None of the definitions of [CON] and [LINKER] include a biotin moiety:



as present in the cited compound from Spiegel. Further, the [CRBM] moiety is defined as



which is not disclosed in Spiegel either expressly or inherently and is wholly different from the CRBM in the cited structure.

Accordingly, Spiegel does not expressly or inherently disclose each and every element of amended claim 1 or 27, and thus it does not anticipate amended claim 1 or 27. Claims 18 and 20-22 are also not anticipated at least by virtue of their dependence from amended claim 1.

Withdrawal of the rejection is respectfully requested.

Response to Rejection under 35 U.S.C. § 103

Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216-5231) in view of Guerrab et al. (Oncotarget. 2016; 7(45): 73618-73637) in view of Buckey et al. (Am J Clin Pathol 2008;129:245-251) in view of Choe et al. (Materials. 2016, 9(12), 994) and evidenced by Zhu et al. (Angew. Chem. Int. Ed. 2023, 62, e202300694) and in view of Semple et al. (Journal of Polymer Science, Part A: Polymer Chemistry. 2016; 54: 2888-2895). This rejection is respectfully traversed.

The rejection of claims 4, 6, 10-11, 15, 23-24, and 28 is moot in view of their cancellation.

The Office argues that a skilled artisan would have found it obvious to combined the

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Attorney Docket No. 047162-7259033 (01855)
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trivalent ASGP-R ligands of Khorev with an Fc-binding peptide allegedly taught by Guerrab in view of Buckley and Choe because:

- a) Khorev shows a trivalent Gal/GalNAc-containing ligands that specifically bind to asialoglycoprotein of hepatocellular carcinoma;
- b) Guerrab and Buckley allegedly teach that overexpression of EGFR has been observed in 40-70% of conventional hepatocellular carcinoma (HCC) cases and that monoclonal antibodies (cetuximab or panitumumab) treat EGFR positive cancer;
- c) Choe allegedly teaches the Fc-binding peptide Fc-III non-covalently attached to an antibody in a drug delivery system.

Applicant respectfully submits that the Office misunderstands the nature of the claimed invention and as a result makes clearly erroneous conclusions. This is evidenced by the statement in the Action that in view of the cited art

“one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to select Khorev's targeting moiety non-covalently linked to Guerrab's anti-cancer antibody (cetuximab or panitumumab) via Choe's high binding affinity of Fc-III to form a complex in a drug delivery system to treat specific hepatocellular carcinoma expressing EGFR and internalize antibody-bound EGFR via Khorev's trivalent Gal/GalNAc targeted asialoglycoprotein receptor for degradation as evidenced by Zhu.” Action, p. 13.

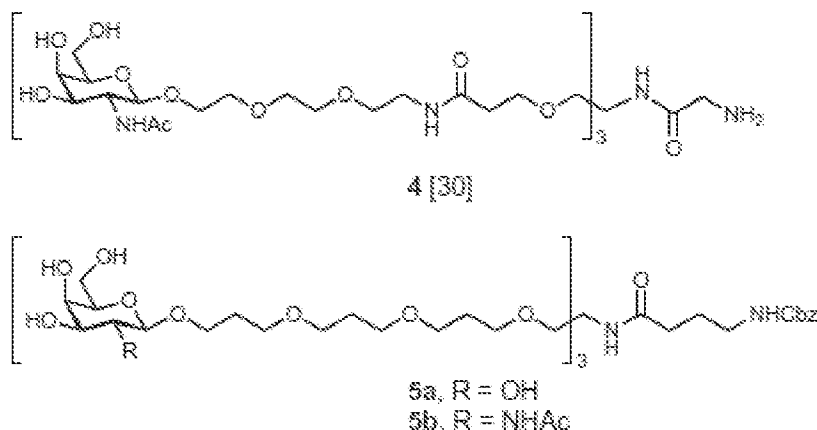
Contrary to the Office's allegation, the present claims are directed to compositions of matter, not methods of treatment, and do not recite or encompass an antibody, much less an anti-cancer antibody.

Indeed, the Office's reasoning is flawed because it is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to the artisan of ordinary skill. *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965). In picking and choosing from the cited references only elements that support its position, the Action relies on **impermissible hindsight** to reconstruct the claimed invention from isolated disclosures in the prior art. *See Ecolchem, Inc. v. S. California Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000) (an Action “cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention”). Respectfully, “[t]he inventor's own path itself never leads to a conclusion of obviousness; that is hindsight.

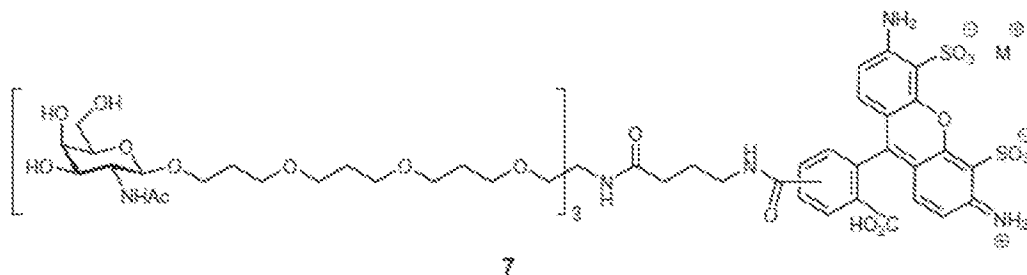
What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art.” *Otsuka Pharm. Co., v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012). “Obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.” *See Univ. of Strathclyde v. Clear-Vu Lighting, LLC*, 17 F.4th 155, 162 (Fed. Cir. 2021). (quoting *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998)). The cited art was misapplied for at least the following reasons.

Khorev describes a variety of trivalent ligands that bind to ASGP-R. *See Khorev*, p. 5217. Khorev provides examples of certain *in vivo* protocols that target ASGP-R, including poly-L-lysine linked asialoorosomucoid, asialofetuin-labeled liposomes that encapsulate plasmid DNA, and liposomal gene carriers that possess synthetic galactose residues. *Id.* None of these examples includes a [CPBM] as defined by amended claim 1 or 27. The stated aim of Khorev is to “synthesize the **optimal** trivalent linker with reduced synthetic complexity, high *in vivo* stability, and improved spacer flexibility.” *Id.* (emphasis added) (internal citations omitted).

Among the trivalent ligands described in Khorev are:



Ligand 4 is from a different reference (not Khorev), while ligands 5a and 5b are from Khorev and correspond to the “optimal” ligand in Khorev. These optimal ligands were linked to fluorescent labels, but not to any therapeutic agents. *See Khorev*, p. 5219. Khorev's optimal ligands use a propylene (C₃) spacer instead of an ethylene spacer. The Office states that Khorev demonstrates that a trivalent Gal/GalNAc is effective at internalizing a conjugated ligand into a HepG2 cell, but the ligand for which the Office presents this data for is compound 7, which has the following structure:



Compound 7 is a conjugated derivative of compound 5b. *See* Action, p. 11. The cellular uptake data described in Figure 5 of Khorev and cited in the Action was obtained with fluorescent derivatives of compounds 5a and 5b, not compound 4. Compounds 5 and 7 both have polypropylene glycol spacers whereas the elected compound has polyethylene glycol spacers and claim 1 is amended, in part, to exclude polypropylene glycol spacers.

Thus, contrary to the Office's assertions, there is no data in Khorev that shows that a trivalent Gal/GalNAc with any combination of the recited [LINKER] and [CON] groups is effective at internalizing a conjugated ligand into a HepG2 cell. In particular, there is no data showing this for compound 4 or a conjugate containing the fluorescent group used in compound 7. Indeed, Khorev states that “the sugar residues have to be in an *optimal* spatial arrangement in order to interact selectively and with high affinity with the native ASGP-R.” Khorev, p. 5222. (emphasis added). This “optimal” arrangement includes the use of a propylene glycol spacer, as shown in compounds 7 and 8 of Khorev, but as noted above propylene glycol spacers are excluded from the scope of the instantly amended claims.

The Office admits that Khorev does not teach a trivalent Gal/GalNAc targeting conjugate further linked to a circulating protein binding moiety [CPBM]. On this basis alone, the *prima facie* case of obviousness must fail. The Office has gone on a fishing expedition to selectively cull portions of the claimed invention from the prior art to stitch together the claimed compounds, and then proclaim that they are obvious. Although Applicant appreciates that the claims are used as basis to search the art, after the search is complete any cited art must speak for itself without the benefit of hindsight. Here, Khorev is silent on using any of the recited [CPBM]'s, and there is no teaching or suggestion to pick out the components recited in the pending claims. Nevertheless, it appears that the Office cites to Guerrab and Buckley to provide a link between using certain antibodies and/or tyrosine kinase inhibitors for the purposes of treating HCC.

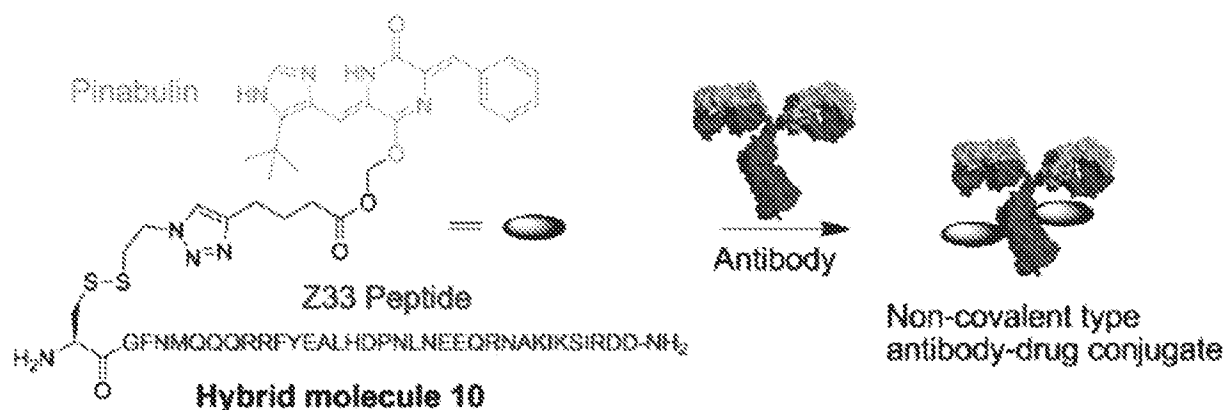
Guerrab describes the synergistic effects of dual targeting EGFR with a monoclonal antibody (cetuximab or panitumumab) and a tyrosine kinase inhibitor (gefitinib or erlotinib). *See* Guerrab, Abstract. In the experiments described in Guerrab, the monoclonal antibodies and tyrosine kinase inhibitors were administered as independent agents as manufactured by the pharmaceutical companies that developed the respective agents; they were not co-formulated, much less covalently linked to anything.

Buckley notes that “efficacy of EGFR antagonists against HCC has been demonstrated in cell lines and animal models. Gefitinib can inhibit growth and intrahepatic metastasis of implanted murine HCC. The benefits of erlotinib, another EGFR TKI, have been demonstrated in phase 2 trials in advanced HCC.” Buckley, p. 245 (internal citations omitted). Buckley describes studies of EGFR expression and overexpression in hepatocellular carcinoma (HCC) and noted that “EGFR overexpression tended to be more common in HCCs arising in cirrhotic liver, but no significant correlation was observed with other clinicopathologic features or survival.” Buckley, p. 249.

Amended claim 1 does not recite any of the antibodies mentioned in Guerrab and Buckley, and indeed it does not recite any antibodies at all: the various [CPBM] moieties recited in claim 1 are not antibodies nor are they tyrosine kinase inhibitors (binders).

The Office appears to cite to Choe in combination with the other art for the concepts of having a triazole moiety in a linker fragment, an Fc binding moiety, and non-covalent interaction of a molecule containing these features with an antibody. As Applicant understands it, the Office asserts that this antibody in Choe is analogous to IgG and the interaction between the Choe hybrid molecule 10 with an antibody is analogous to the interaction of the CRBM with IgG, for example. Applicant respectfully suggests that this conclusion is erroneous. The antibody in Choe is an externally introduced engineered agent, whereas IgG is an endogenously present molecule secreted by the body. Further, as noted elsewhere herein, the pending claims recite compositions of matter that are not disclosed or suggested by the cited art.

Choe describes, in part, applications of immunoglobulin binding ligands such as Fc-III. *See* Choe, p. 9. Choe describes a non-covalent antibody-drug conjugate that uses the high affinity Fc-binding peptide Z33, the anticancer agent plinabulin covalently linked to Z33 by means of a linker, and the anti-Her2 antibody Herceptin, which is schematically shown as:



This antibody-drug conjugate is shown to exhibit cytotoxicity against the SKBR-3 (breast cancer), MCF-7 (breast cancer), SKBR-3HR (breast cancer), and A375 (melanoma) cell lines. See Choe, pp. 12-13.

The pending claims do not recite pinabulin or Choe's Z33 peptide. The Office alleges that

- (a) Khorev teaches the use of trivalent asialoglycoprotein receptor targeting moiety for site-specific drug delivery to the human hepatocellular carcinoma,
- (b) Choe suggests the beneficial use of an Fc-binding peptide conjugate non-covalently binds to an antibody in a drug delivery system, and
- (c) Guerrab in view of Buckley suggest monoclonal antibody (cetuximab or panitumumab) able to treat EGFR expressing cancers (breast cancer and hepatocellular carcinoma).

According to the Office, one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to select Khorev targeting moiety non-covalently linked to Guerrab's anti-cancer antibody (cetuximab or panitumumab) via Choe's high binding affinity of Fc-III to form a complex in a drug delivery system to treat specific hepatocellular carcinoma expressing EGFR and internalize antibody bound EGFR via Khorev's trivalent Gal/GalNAc targeted asialoglycoprotein receptor for degradation as evidenced by Zhu. (Action, p. 13).

The Office's reasoning is flawed for several reasons. First, Khorev does not describe the use of a *therapeutic* agent linked to a trivalent Gal/GalNAc asialoglycoprotein receptor targeting moiety, but merely a fluorescent agent for detection purposes. There is no description or

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suggestion in Khorev of any of the recited [CPBM]'s being bound to anything, much less a trivalent Gal/GalNAc asialoglycoprotein receptor targeting moiety.

Secondly, the system of Choe is wholly unrelated to the claimed invention. The Office appears to be imputing a method of treatment onto plain composition of matter claims. The expressly recited [CPBM]'s do not encompass pinabulin or Choe's Z33 peptide. The "hybrid molecule 10" from Choe is not encompassed by the pending claims and does not render them *prima facie* obvious in view of any of the cited art. Choe indicates that hybrid molecule 10 binds to Herceptin (or the antibody 6E1) in a non-covalent fashion, but the pending claims do not recite these antibodies nor is there any teaching or suggestion in the art that the claimed compounds would bind to Herceptin or 6E1, to the extent that is even relevant. Accordingly, the statement in the Action that "Choe et al. teach the use of an Fc binding peptide (Fc-III, DCAWHLGELVWCTNH₂) for non-covalently attached to an antibody to generate a drug delivery system" is clear error as shown herein. (Action, p. 17). The Fc binding peptide in Choe that is shown to non-covalently attach to an antibody is Z33, which has the sequence GFNMQQRRFYREALHDPNLNEEQRNAKIKSIRDD-NH₂. See Choe, p. 13, Scheme 1.

Finally, Guerrab in view of Buckley describes the use of monoclonal antibodies cetuximab or panitumumab to treat HCC in EGFR-expressing tissues. Although Applicant reiterates that therapeutic antibodies are not encompassed by the pending claims, Guerrab in view of Buckley describe either antibody monotherapy with cetuximab or panitumumab, or a combination therapy of these antibodies with a tyrosine kinase inhibitor.

In summary, Applicant submits that the prior art of record does not render obvious the present claims, and respectfully requests withdrawal of the present rejection.

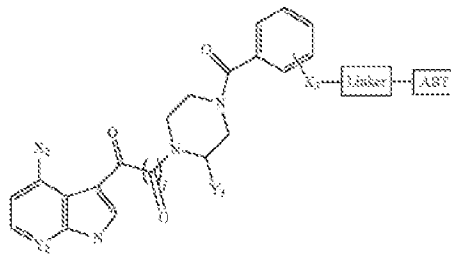
Response to Rejection for Double Patenting

1. Rejection over U.S. Patent No. 9,181,224 and Choe

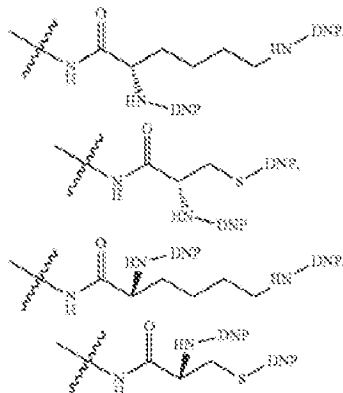
Claims 1, 18, and 20-22 stand rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1 and 6 of U.S. Patent No. 9,181,224 ("the '224 patent") in view of Choe. This rejection is respectfully traversed.

Claim 1 of the '224 patent recites a compound with the following structure:

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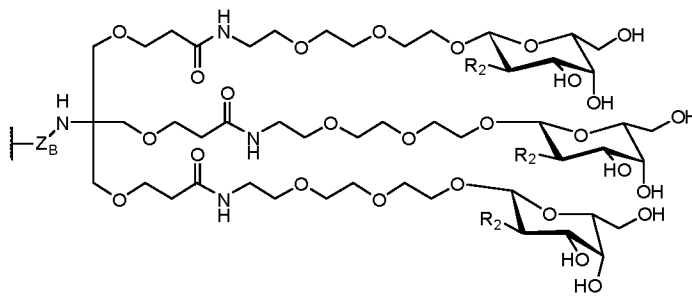


The structure of ABT, as recited in claim 1 of the '224 patent is:



The Office admits that the '224 patent does not specify an antibody binding moiety such as Fc-III, and to allegedly cure this defect cites to Choe for its disclosure of Fc-III as an antibody binding peptide to “make the compound [Fc-III]-linker-[CD4 cellular receptor binding domain].”

Amended claim 1 does not encompass a compound with the structure [Fc-III]-linker-[CD4 cellular receptor binding domain] at least because amended claim 1 requires a [CRBM] with the structure:



which is not described or suggested in the '224 patent or in Choe.

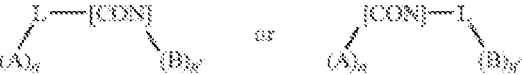
Accordingly, present claims 1, 18, and 20-22 are patentably distinct from the combination of the '224 patent and Choe.

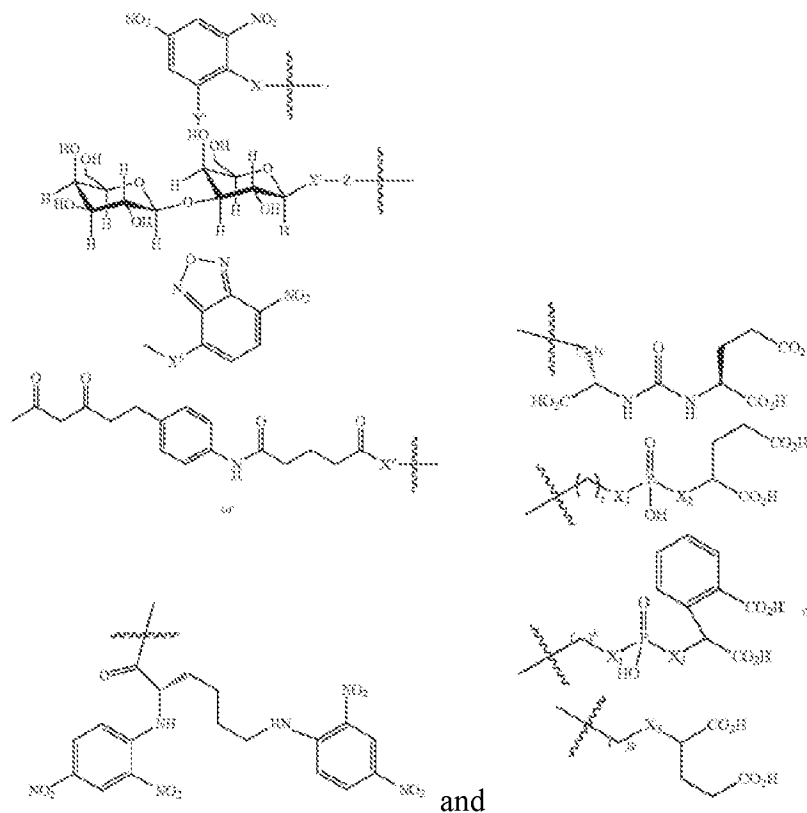
Withdrawal of the rejection is respectfully requested.

2. *Rejection over U.S. Patent No. 9,296,708 and Choe*

Claims 1, 18, 20-22, and 27 stand rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 6, and 20 of U.S. Patent No. 9,296,708 (“the ‘708 patent”) in view of Choe. This rejection is respectfully traversed.

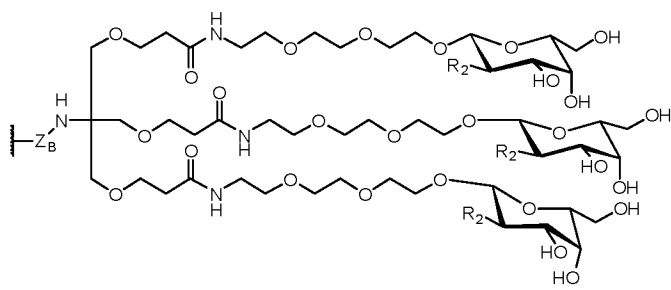
Claim 1 of the ‘708 patent recites a compound with the general structure:

 , with A and B having the following structures, respectively:



The Office admits that the ‘708 patent does not specify an antibody binding moiety such as Fc-III, and to allegedly cure this defect cites to Choe for its disclosure of Fc-III as an antibody binding peptide to “make the compound [Fc-III]-Spacer-[cellular receptor binding domain].”

Amended claim 1 does not encompass a compound with the structure [Fc-III]-Spacer-[cellular receptor binding domain] at least because amended claim 1 requires a [CRBM] with the structure:



which is not described or suggested in the '708 patent or in Choe.

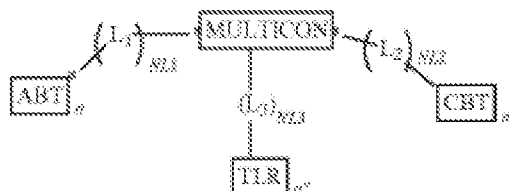
Accordingly, present claims 1, 18, 20-22, and 27 are patentably distinct from the combination of the '708 patent and Choe.

Withdrawal of the rejection is respectfully requested.

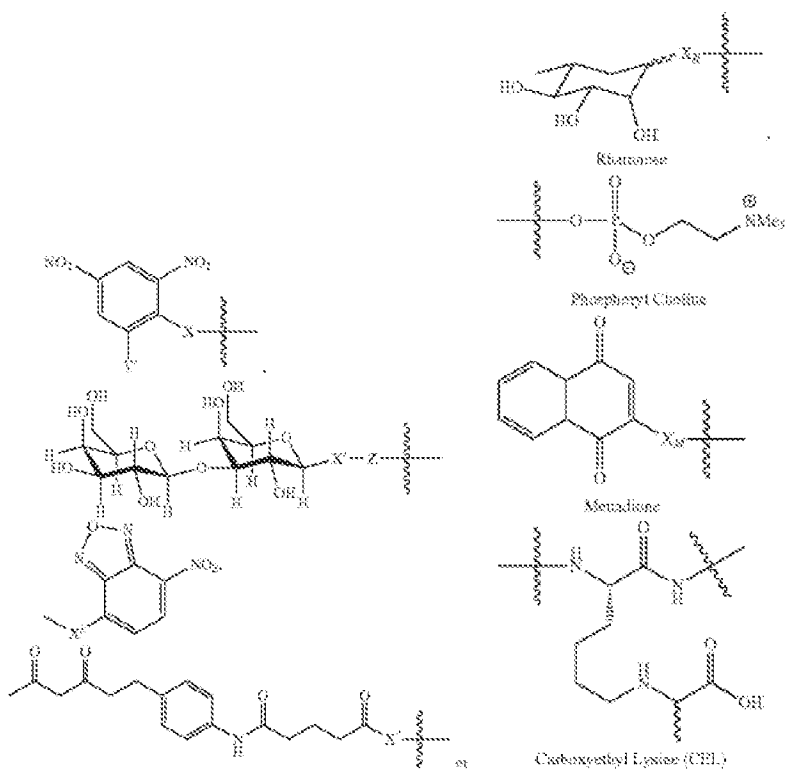
3. Rejection over U.S. Patent No. 9,556,167 and Choe

Claims 1, 18, 20-23, and 27 stand rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-2, 18, 26, and 32 of U.S. Patent No. 9,556,167 ("the '167 patent") in view of Choe. This rejection is respectfully traversed.

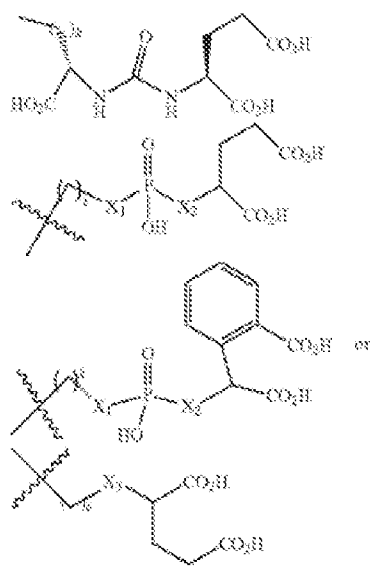
Claim 1 of the '167 patent recites a compound with the general structure:



wherein ABT has the structure

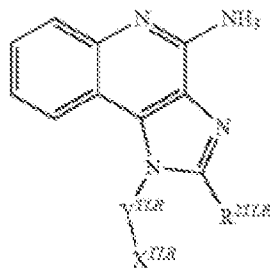


[CBT] has the structure



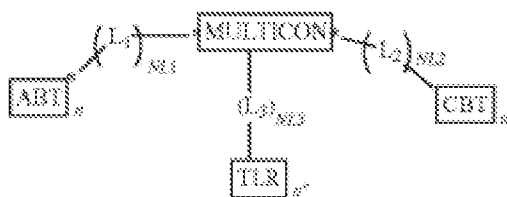
, and

[TLR] has the structure

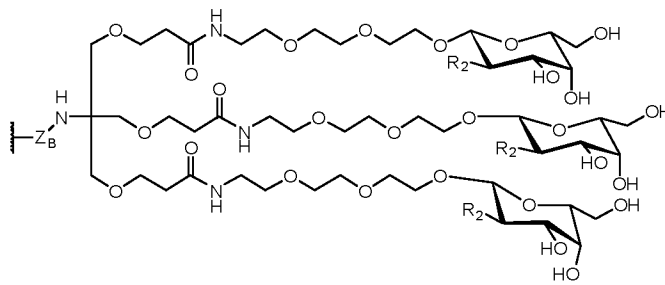


The Office admits that the '167 patent does not specify an antibody binding moiety such as Fc-III, and to allegedly cure this defect cites to Choe for its disclosure of Fc-III as an antibody binding peptide.

Amended claim 1 does not encompass a compound with the structure



at least because amended claim 1 requires a [CRBM] with the structure:



which is not described or suggested in the '167 patent or in Choe. Further, the compound recited in amended claim 1 does not include a [TLR] fragment (TLR-binding fragment), which is a required feature of the the compound in the '167 patent.

Accordingly, present claims 1, 18, 20-22, and 27 are patentably distinct from the combination of the '167 patent and Choe.

Withdrawal of the rejection is respectfully requested.

4. Rejection over U.S. Patent No. 10,066,026 and Choe

Claims 1, 18, 20-22, and 27 stand rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1 and 21 of U.S. Patent No. 10,066,026 ("the '026

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patent”) in view of Choe. This rejection is respectfully traversed.

Present claims 1, 18, 20-22, and 27 are patentably distinct over claims 1 and 21 of the '026 patent for substantially the same reasons as for the '708 patent, as noted herein. The '026 patent does not teach or suggest the trivalent asialoglycoprotein receptor targeting moiety recited in amended claim 1.

Withdrawal of the rejection is respectfully requested.

5. *Rejection over U.S. Patent No. 10,016,412 and Choe*

Claims 1, 18, 20-22, and 27-28 stand rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 14, 23-24, and 26 of US 10,016,412 (“the '412 patent”) in view of Choe. This rejection is respectfully traversed.

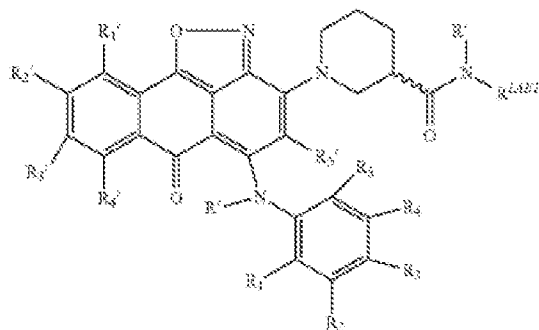
Present claims 1, 18, 20-22, and 27 are patentably distinct over claims 1, 14, 23-24, and 26 of the '412 patent for substantially the same reasons as for the '167 patent, as noted herein. The '412 patent does not teach or suggest the trivalent asialoglycoprotein receptor targeting moiety recited in amended claim 1. Further, the '412 patent requires the presence of a TLR-binding group which is excluded from the scope of the genus defined in amended claim 1 or 27.

Withdrawal of the rejection is respectfully requested.

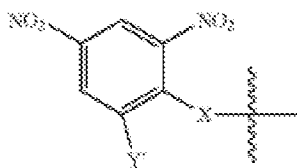
6. *Rejection over U.S. Patent No. 10,633,374 and Choe*

Claims 1, 18, 20-22, and 27-28 stand rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 14, 23-24, and 26 of U.S. Patent No. 10,633,374 (“the '374 patent”) in view of Choe. This rejection is respectfully traversed.

Claim 1 of the '374 patent recites a compound with the following structure:



and the R^{LABT} group includes a linker and a group with the structure:



Neither Choe nor the '374 patent teach or suggest the trivalent asialoglycoprotein receptor targeting moiety recited in amended claim 1 or 27. Thus, present claims 1, 18, 20-22, and 27 are patentably distinct over claims 1, 14, 23-24 and 26 of the '374 patent.

Withdrawal of the rejection is respectfully requested.

7. Rejection over U.S. Patent No. 10,703,823 and Choe

Claims 1, 18, 20-22, and 27-28 stand rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 14, 23-24 and 26 of U.S. Patent No. 10,703,823 (“the '823 patent”) in view of Choe. This rejection is respectfully traversed.

Present claims 1, 18, 20-22, and 27 are patentably distinct over claims 1, 14, 23-24 and 26 of the '823 patent for substantially the same reasons as for the '708 patent, as noted herein. Neither the '823 patent nor Choe teach or suggest the trivalent asialoglycoprotein receptor targeting moiety recited in amended claim 1 or 27.

Withdrawal of the rejection is respectfully requested.

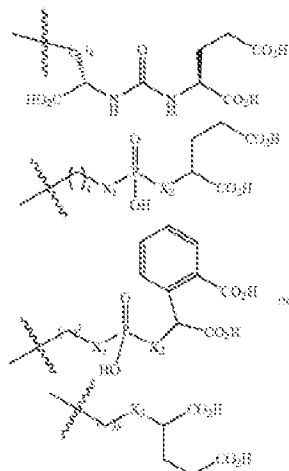
8. Rejection over U.S. Patent No. 10,912,836

Claims 1, 18, 20-22, and 27-28 stand rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 14, 23-24 and 26 of US 10,912,836 (“the '836 patent”) in view Choe. This rejection is respectfully traversed.

Claim 1 of the '836 patent recites the following general structure:



where IBT is a FcγRI receptor binding moiety and CBT is a moiety that binds to prostate specific membrane antigen (PSMA) and having the structure:



Neither Choe nor the '836 patent teach or suggest the trivalent asialoglycoprotein receptor targeting moiety recited in amended claim 1 or 27. Thus, present claims 1, 18, 20-22, and 27 are patentably distinct over claims 1, 14, 23-24 and 26 of the '836 patent.

Withdrawal of the rejection is respectfully requested.

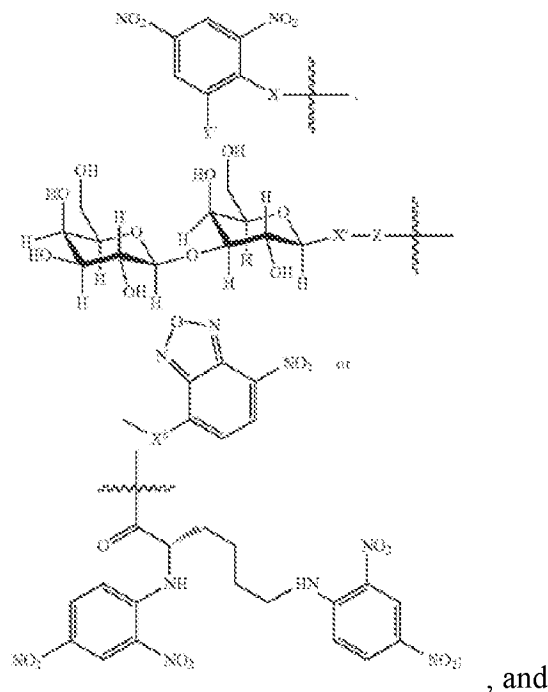
9. Rejection over U.S. Patent No. 11,014,992 and Choe

Claims 1, 18, 20-23, and 27 stand rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 10, and 16 of US 11,014,992 ("the '992 patent") in view Choe. This rejection is respectfully traversed.

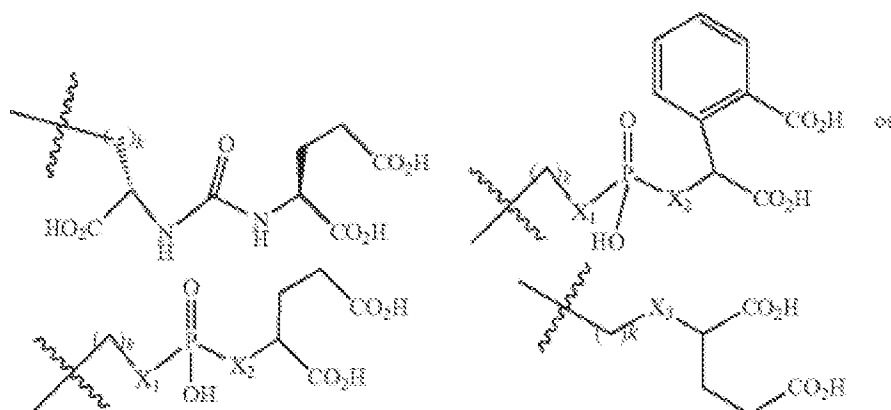
Claim 1 of the '992 patent recites a compound having the general structure:



wherein A is:



B is



Neither Choe nor the '992 patent teach or suggest the trivalent asialoglycoprotein receptor targeting moiety recited in amended claim 1 or 27. Thus, present claims 1, 18, 20-23, and 27 are patentably distinct over claims 1, 10, and 16 of the '992 patent.

Withdrawal of the rejection is respectfully requested.

10. Rejection over U.S. Patent No. 11,725,064 and Choe

Claims 1, 18, 20-23, and 27 stand rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 10, and 16 of U.S. Patent No. 11,725,064 (“the '064 patent”) in view of Choe. This rejection is respectfully traversed.

Present claims 1, 18, 20-23, and 27 are patentably distinct over claims 1, 10, and 16 of the '064 patent for substantially the same reasons as for the '992 patent, as noted herein. Neither the '064 patent nor Choe teach or suggest the trivalent asialoglycoprotein receptor targeting moiety recited in amended claim 1 or 27.

Withdrawal of the rejection is respectfully requested.

11. Provisional Rejections Over Co-Pending Applications

The following pending claims stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over the following co-pending applications and claims:

- i. claims 1, 18, 20, 22-23, and 27 stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 20, and 66 of co-pending Application No. 16/634,032;
- ii. claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 12, 33, and 37 of co-pending Application No. 17/046,192;
- iii. claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4, 6, 10, 12, 18, 24, 29-30, 32, and 37 of co-pending Application No. 17/046,221;
- iv. claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27 stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 15-16, 19-20, 23, 27, and 30 of co-pending Application No. 17/654,990;
- v. claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3, 5, 9-10, 14, 16, 18, 21-23, and 26-27 of co-pending Application No. 17/695,259;
- vi. claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4, 6, 10-11, 15, 18, 20-24, and 28 of co-pending Application No. 17/695,645;
- vii. claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27 stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3, 9-10, 14, 16, 18, 21-23, and 26-27 of co-pending Application No. 18/161,633; and
- viii. claims 1, 18, 20-23 and 27-28 stand provisionally rejected on the ground of nonstatutory

U.S. Patent Application No. [REDACTED]

Attorney Docket No. 047162-7239US (01833)

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double patenting as being unpatentable over claims 1, 12-13, 23, and 26 of co-pending Application No. 18/206,937.

Applicant respectfully requests that double patenting rejections (i)-(viii) be held in abeyance until allowable subject matter is indicated.

U.S. Patent Application No.

Attorney Docket No. 047162-7239US (01833)

Response to non-final Office Action issued September 11, 2023

Summary

Early consideration and allowance of the claims in the present application is requested at the earliest possible time.

Respectfully submitted,

DAVID SPIEGEL, *et al.*

December 11, 2023

Date

By: /Dennis Ostrovsky/

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Attorney for Applicant

DO

EXHIBIT 17



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/161,712	01/30/2023	David Spiegel	047162-7239US3(01833)	9168
78905	7590	01/11/2024	EXAMINER	
Saul Ewing LLP (Philadelphia)			LEE, JIA-HAI	
Attn: Patent Docket Clerk			ART UNIT	
Centre Square West			PAPER NUMBER	
1500 Market Street, 38th Floor			1658	
Philadelphia, PA 19102-2186			NOTIFICATION DATE	
			DELIVERY MODE	
			01/11/2024	
			ELECTRONIC	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@saull.com

Office Action Summary

18/161,712

Applicant(s)

Spiegel et al.

Examiner

JIA-HAI LEE

Art Unit

1658

AIA (FITF) Status

Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 12/11/2023.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2a) ☒ This action is **FINAL**.

2b) ☐ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-2,16-18,20-22 and 26-27 is/are pending in the application.

5a) Of the above claim(s) 16-17 and 26 is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☒ Claim(s) 1-2,18,20-22 and 27 is/are rejected.

8) ☐ Claim(s) ____ is/are objected to.

9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date ____.

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: ____.

Paper No(s)/Mail Date 10/24/2023,12/11/2023.

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DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Status

Claims 1-2, 16-18, 20-22, and 26-27 are pending.

Claims 3, 9, 19, 25, and 28 are cancelled.

Claims 16-17, and 26 are withdrawn as being directed to a non-elected invention, the election having been made on 7/31/2023. Claim 2 is rejoined as the combined prior art references teach the limitation.

Claims 1-2, 18, 20-22, and 27 have been examined.

Priority

This application is a CON of 17/695,645 filed on 03/15/2022

17/695,645 is a CIP of 17/046,221 filed on 10/08/2020

17/046,221 is a 371 of PCT/US2019/026260 filed on 04/08/2019

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 10/24/2023 and 12/11/2023 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

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Withdrawn Objection

The objection to claim 6 is withdrawn because applicant canceled claims 4 and 6.

Claims 1, 4, 6, 10-11, 15, 18, 20-24, and 27-28 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, is withdrawn because the amendment to claim 1 overcomes the rejection of record.

The rejection claims 1, 18, 20, 23, and 27-28 under 35 U.S.C. 102(a)(1) and (a)(2) as being anticipated by Spiegel et al. is withdrawn because the amendment to claim 1 overcomes the rejection of record.

The rejection of claims 1, 18, 20-22, and 27-28 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 14, 23-24 and 26 of U.S. Patent No. 10,912,836 B2 is withdrawn because the amendment overcomes this rejection.

Modified Rejection

Improper Markush Grouping

Claims 1-2, 18, and 27 are rejected on the basis that they contain an improper Markush grouping of alternatives. See *In re Harnisch*, 631 F.2d 716, 721-22 (CCPA 1980) and *Ex parte Hozumi*, 3 USPQ2d 1059, 1060 (Bd. Pat. App. & Int. 1984). A Markush grouping is proper if the alternatives defined by the Markush group (i.e., alternatives from which a selection is to be made in the context of a combination or process, or alternative chemical compounds as a whole) share a “single structural similarity” AND a common use. A Markush grouping meets these requirements in two situations. First, a Markush grouping is proper if the alternatives are all members of the same recognized physical or chemical class or the same art-recognized class, and are disclosed in the specification or known in the art to be functionally equivalent and have a

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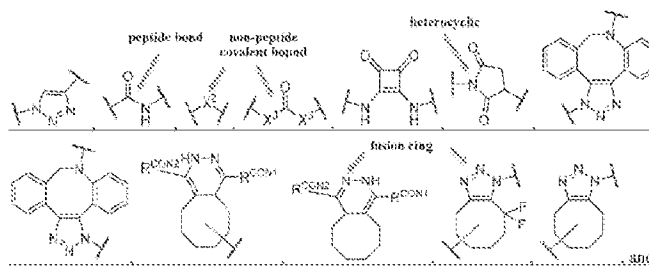
common use. Second, where a Markush grouping describes alternative chemical compounds, whether by words or chemical formulas, and the alternatives do not belong to a recognized class as set forth above, the members of the Markush grouping may be considered to share a “single structural similarity” and common use where the alternatives share both a substantial structural feature AND a common use that flows from the substantial structural feature. See MPEP § 706.03(y).

The Markush grouping of CPBM and CON is improper because the alternatives defined by the Markush grouping do not share both a single structural similarity and a common use for the following reasons:

The CPBM moieties (a) to (k) comprise non-peptidyl compounds, saccharide, and distinct peptide sequences, but they are not the same art-recognized class with same recognized physical or chemical properties. Furthermore, the compound moieties (a) to (k) do not share a “single structural similarity” even though they appear to have a common use for binding to a cellular protein. For instance, CPBM (k) shown as follows comprises various structurally distinct polypeptide sequences with different physical or chemical properties, rendering CPBM (k) itself is also an improper Markush grouping. Thus, the Markush grouping of CPBM is improper.

PAM;
D-PAM;
D-PAM-Φ;
TWKTSRISIF (SEQ ID NO.1);
FGRLVSSIRY (SEQ ID NO.2);
Fc-III;
FcBP-1;
FcBP-2;
Fc-III-4c;
EPHRSILTALL (SEQ ID NO.3);
APAR (SEQ ID NO.4);
FcRM;
HWRGWV (SEQ ID NO.5);
HYFKFD (SEQ ID NO.6);
HFRRHL (SEQ ID NO.7);

The CON moieties a, b, and c comprise various compound structures but they are not the same art-recognized class with same recognized physical or chemical properties. See examples of a claimed CON moiety of comprising a single heterocyclic, a peptide



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bond, a non-peptide covalent bond, fusion rings above. These compound structures fail to share a “single structural similarity” as required for Markush grouping; thus, the Markush grouping of CON is also improper.

To overcome this rejection, Applicant may set forth each alternative (or grouping of patentably indistinct alternatives) within an improper Markush grouping in a series of independent or dependent claims and/or present convincing arguments that the group members recited in the alternative within a single claim in fact share a single structural similarity as well as a common use.

Response to Arguments

Applicant's arguments of the amendments overcoming the improper Markush grouping rejection filed 12/11/2023 (Remarks, p62 to 63, Response to Rejection for Improper Markush Group) have been fully considered but they are not persuasive because the CPBM moieties (a) to (k) comprise non-peptidyl compounds, saccharide, and distinct peptide sequences, but they are not the same art-recognized class with same recognized physical or chemical properties. Furthermore, the compound moieties (a) to (k) do not share a “single structural similarity” even though they appear to have a common use for binding to a cellular protein. Thus, the Markush grouping of CPBM is improper.

In summary, the compounds of CPBM moieties and CON structures do NOT share a “single structural similarity” and/or in the same art-recognized class with same physical or chemical properties. The rejection will be maintained until applicant's amendments to satisfy the requirements of proper Markush grouping described above.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 18, 20-22, and 27 are rejected under 35 U.S.C. 103 as being unpatentable over Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.) in view of Guerrab et al. (Oncotarget. 2016; 7(45): 73618-73637) in view of Buckey et al. (Am J Clin Pathol 2008;129:245-251.) in view of Choe et al. (Materials. 2016, 9(12), 994) and evidenced by

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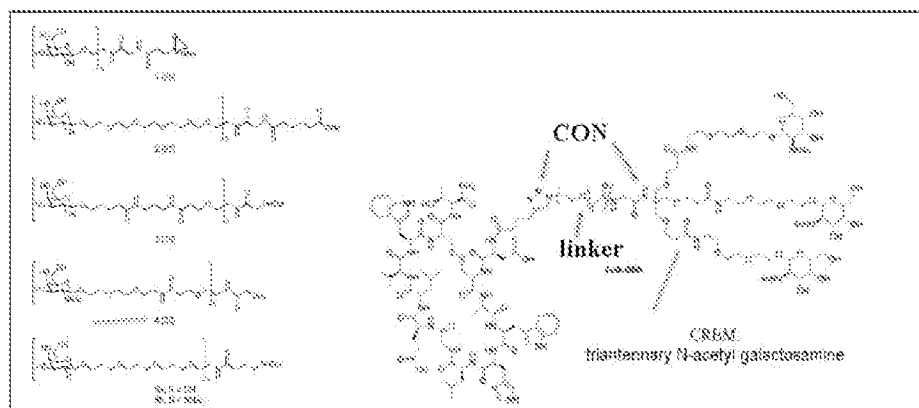
Zhu et al. (Angew. Chem. Int. Ed. 2023, 62, e202300694) and in view of Semple et al. (Journal of Polymer Science, Part A: Polymer Chemistry. 2016; 54: 2888–2895.)

Claim 1 is drawn to a bifunctional compound formula shown as follows



Khorev et al. teach “Trivalent, Gal/GalNAc-containing ligands designed for the asialoglycoprotein receptor” (Title). Khorev et al. teach triantennary ligands displayed a higher affinity than their mono- and diantennary counterparts. Khorev et al. further teach only the terminal residues are necessary for specific recognition, and that the binding process proceeds through a simultaneous interaction of 2–3 sugar residues with 2–3 binding sites of the heterooligomeric receptor of asialoglycoprotein receptor/ASGP-R (p5216, col 2, last para bridging to p5217, col 1, para 1) shown in figure 1 above. Khorev et al. show triantennary ligands targeted to ASGP-R below (p5218, Fig 2),

suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG)



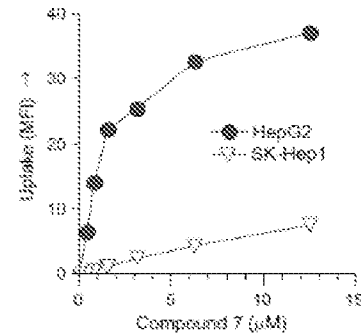
and/or amide bond do not significantly affect the terminal galactose and N-acetylgalactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev’s trivalent asialoglycoprotein receptor targeting moiety compound 4 reads on the GN3 moiety of elected species as follows. Khorev et al. demonstrate a trivalent Gal/GalNAc targeting ligand is more effective to internalize a conjugated compound into an asialoglycoprotein receptor (ASGP-R) positive human

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hepatocellular carcinoma HepG2 cell than an ASGP-R negative SK-Hep1 cells as follows (p5222, Fig 5). Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1).



Khorev et al. do not teach a trivalent Gal/GalNAc targeting conjugate further linked to a circulating Protein Binding Moiety (CPBM).

Guerrab et al. teach administration of monoclonal antibody, cetuximab or panitumumab, and/or one tyrosine kinase inhibitor (EGFR-TKI; gefitinib or erlotinib) as a targeted therapy to treat cancer cells overexpression of epidermal growth factor receptor (EGFR) known in the art (Abstract). Similarly, Buckley et al. teach overexpression of epidermal growth factor receptor (EGFR) has been observed in around 40% to 70% of conventional Hepatocellular carcinoma (HCC) in most studies. Buckley et al. further suggest administration of tyrosine kinase inhibitor (EGFR TKIs) anti-EGFR antibodies to treat EGFR expressing cancers (p245, col 2, para 2).

Because (a) Hepatocellular carcinoma (HCC) overexpresses epidermal growth factor receptor (EGFR) and (b) Guerrab et al. teach administration of monoclonal antibody, cetuximab or panitumumab, and/or one tyrosine kinase inhibitor (EGFR-TKI; gefitinib or erlotinib) to treat cancer cells overexpression of epidermal growth factor receptor (EGFR) as a common knowledge known in the art, one of ordinary skill in the art before the effective filing date of this invention would have found it obvious to administration Guerrab's monoclonal antibody of cetuximab or panitumumab to treat hepatocellular carcinoma or breast cancer overexpression of epidermal growth factor receptor (EGFR). Choe et al. teach Fc-binding ligand of immunoglobulin G (Title). Choe et al. teach a 13-mer Fc binding peptide (Fc-III,

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DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards the Fc-region of IgG was identified via phage

display (p6, para 3), reading on the elected species of Fc-III shown above. Choe et al.

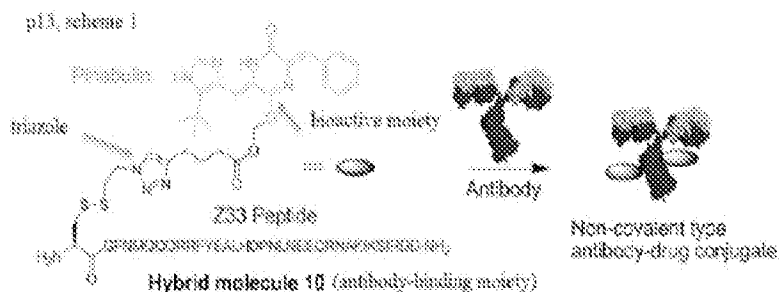
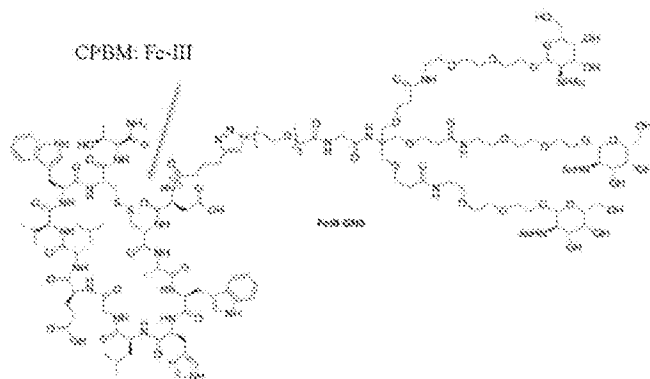
show an antibody binding moiety is non-covalently bind to Fc region of an antibody

and further suggest the use triazole as a linking moiety resulting from click chemistry reaction shown below (p13, scheme 1), suggesting that (bioactive agent)-Triazole-(Fc-binding peptide)--Antibody can form a complex in a single drug delivery system. Because (a) Khorevet et al. teach the use of trivalent asialoglycoprotein receptor targeting moiety for site-specific drug delivery to the human hepatocellular

carcinoma (Abstract; p5220, col 2, 3. Biological evaluation), (b)

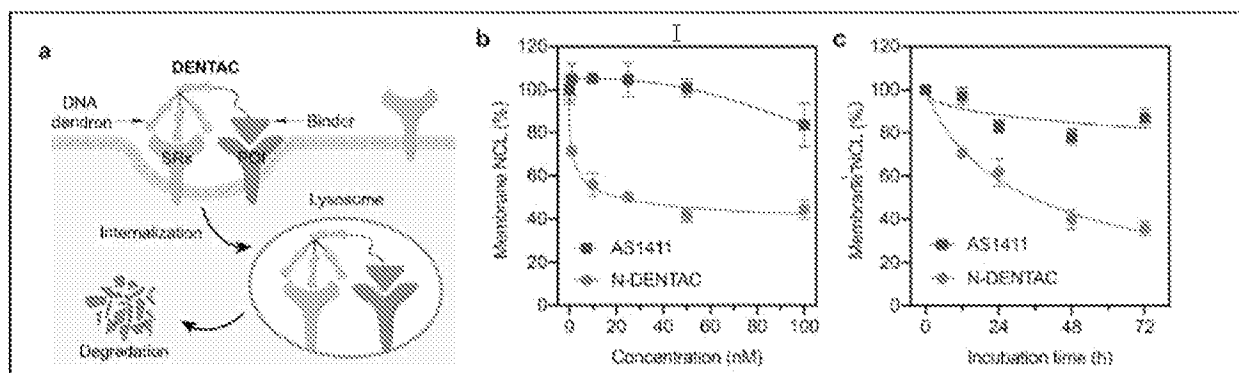
Choe et al. suggest the beneficial

use of an Fc-binding peptide conjugate non-covalently binds to an antibody in a drug delivery system, and (c) Guerrab et al. in view of Buckley et al. suggest monoclonal antibody (cetuximab or panitumumab) able to treat EGFR expressing cancers (breast cancer and hepatocellular carcinoma), one of ordinary skill in the art before the effective filing date of the invention would have found it obvious to select Khorevet's targeting moiety non-covalently linked to Guerrab's anti-cancer antibody (cetuximab or panitumumab) via Choe's high binding affinity of Fc-III to form a complex in a drug delivery system to treat specific hepatocellular carcinoma expressing EGFR and internalize antibody-bound EGFR via Khorev's trivalent Gal/GalNAc targeted asialoglycoprotein receptor for degradation as evidenced by Zhu et al. (p2, scheme 1a & p3, Fig



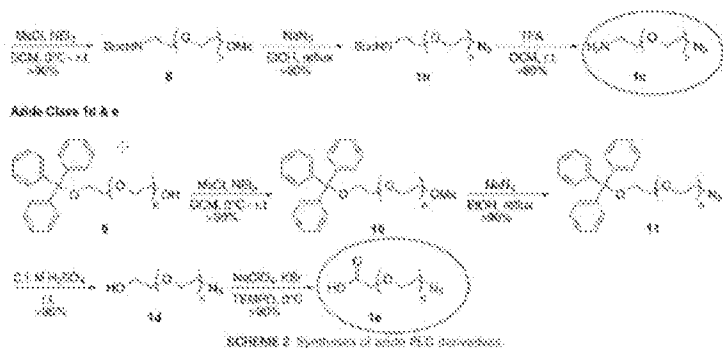
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2b-2c) shown as follows.



Khorev et al. in view of Guerrab et al. in view of Buckey et al. and in view of Choe et al. and evidenced by Zhu et al. do not explicitly teach a PEG linker functionalized with click chemistry reactive moiety to link Choe's Fc-binding peptide and Khorevet's targeting moiety together via a triazole moiety.

Sample et al. teach Poly(ethylene glycol) (PEG) derivatives have been applied in bioconjugation chemistry through the modification of peptides and proteins for drug delivery. Sample et al. suggest incorporation of PEG-containing moieties (PEGylation) into



such systems generally improves pharmacological properties including increased water solubility, enhanced resistance to protein hydrolysis/degradation, improved bioavailability (circulation half-life), and reduced antigenicity (p2888, col 1, Introduction). Semple et al. show synthesis of azido PEG derivative of compound 1c and 1e above (p2892, scheme 2). Semple et al. further show a click chemistry reaction for azido functionalized PEG derivative covalently linked to the counterpart click chemistry reactive moiety comprising to form triazole as follows (p2889, scheme 1). Khorev et al. show a PEG repeating unit is 3 (e.g., compound 4 of Fig 2

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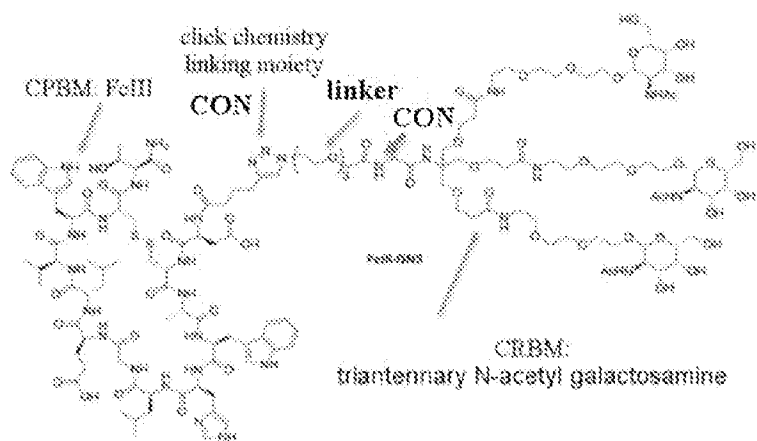
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shown above). Because Semple et al. teach various advantages of using PEG derivatives in bioconjugation chemistry for drug delivery (p2888, col 1, Introduction), one of ordinary skill in the art before the effective filing date of this invention would have found it obvious to beneficial use Semple's azido PEG derivative (compound 1e) as a bi-functional linker comprising a carboxylic group reacting to the amine group of Khorev's cell targeting moiety and an azido group reacting to acetylene functionalized Fc-III to form a triazole connecting moiety, reading on the elected species structure in claims 1-2.

One of ordinary skill in the art before the effective filing date of this invention would have found it obvious to combine Khorev's triantennary N-acetyl-galactosamine (CRMB) with Fc-binding peptide of CPBM taught by Guerrab et al. in view of Buckey et al. and Choe et al. because (a) Khorev et al. show trivalent Gal/GalNAc-containing ligands specifically binding to the asialoglycoprotein receptor of hepatocellular carcinoma (p5812, Fig 2; p5220, col 2, 3. Biological evaluation), (b) Guerrab et al. and Buckley et al. teach the common knowledge of (b)(i) overexpression of epidermal growth factor receptor (EGFR) has been observed in around 40% to 70% of conventional

Hepatocellular carcinoma (HCC) taught by Buckley et al. (p245, col 2, para 2) and (b)(ii) the use of monoclonal antibodies (cetuximab or panitumumab) to treat EGFR

positive cancer taught by Guerrab et al. (Abstract), and (c) Choe et al. teach the use of an Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) for non-covalently attached to an antibody in a drug delivery system (p13, scheme 1). The combination would have reasonable



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expectation of success because the references teach targeted therapy of a drug delivery system comprising a cellular targeting moiety, an antibody binding moiety, and an anti-cancer drug (either an antibody or small a molecule compound).

One of ordinary skill in the art before the effective filing date of this invention would have found it further obvious to combine Khorev et al. in view of Guerrab et al. in view of Buckey et al. and in view of Choe et al. evidenced by Zhu et al. with Semple's azido PEG spacer because (a) Khorev et al. in view of Guerrab et al. in view of Buckey et al. and in view of Choe et al. evidenced by Zhu et al. teach (triantennary ligands targeting moiety)-Triazole-(Fc-binding peptide)--Antibody forming a complex in a drug delivery system and (b) Semple et al. suggest beneficial incorporation of PEG-containing moieties (PEGylation) into such systems generally improves pharmacological properties including increased water solubility, enhanced resistance to protein hydrolysis/degradation, improved bioavailability (circulation half-life), and reduced antigenicity (p2888, col 1, Introduction) and show the use of azido PEG derivative for click chemistry to generate a conjugate via a connecting moiety of triazole (p2889, scheme 1). The combination would have reasonable expectation of success because both Choe et al. and Semple et al. teach the use of click chemistry to combine two moieties to form a conjugate via a click chemistry connecting moiety of triazole.

With respect to claim 18, Choe et al. teach the use of an Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) for non-covalently attached to an antibody in a drug delivery system (p13, scheme 1).

With respect to claims 20 and 22, Semple et al. show an azido PEG derivative linker (p2892, scheme 2) comprising the structure as reading polyethylene glycol units between 1 and 100. Khorev et al. further show a PEG repeating unit is n=3 (e.g., compound 4 of Fig 2).

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With respect to claim 21, Khorev's compound 4 comprises free amine group reacting to a carboxylic group of azido PEG derivative linker to form an amide bond (NH-CO), reading on Ram=H and na=0.

With respect to claim 27, Choe et al. teach Fc-binding peptide conjugate pre-mixed with antibody in a carrier solvent before injection (p12, Fig 9, legend).

Applicant's Argument

- (i) Contrary to the Office's allegation, the present claims are directed to compositions of matter, not methods of treatment, and do not recite or encompass an antibody, much less an anticancer antibody. The rejection relies on impermissible hindsight (Remarks, p65, para 4-5 to p66, para 1).
- (ii) There is no data in Khorev that shows that a trivalent Gal/GalNAc with any combination of the recited [LINKER] and [CON] groups is effective at internalizing a conjugated ligand into a HepG2 cell. Khorev does not teach a trivalent Gal/GalNAc targeting conjugate further linked to a circulating protein binding moiety [CPBM] (Remarks, p66, para 2-3 to p67).
- (iii) Guerrab's monoclonal antibodies and tyrosine kinase inhibitors were administered as independent agents; they were not co-formulated much less covalently linked to anything (Remarks, p68, para 1).
- (iv) Buckley describes studies of EGFR expression and overexpression in hepatocellular carcinoma (HCC) and noted that "EGFR overexpression tended to be more common in HCCs arising in cirrhotic liver, but no significant correlation was observed with other clinicopathologic features or survival." Buckley, p. 249. (Remarks, p68, para 2).
- (v) Choe is analogous to IgG and the interaction between the Choe hybrid molecule 10 with an antibody is analogous to the interaction of the CRBM with IgG, for example. Applicant

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respectfully suggests that this conclusion is erroneous because Choe's antibody is an engineered antibody whereas IgG is an endogenously present molecule secreted by the body (Remarks, p68, para 4-5 to p69, para 1).

(vi) The Office's reasoning is flawed for several reasons. First, Khorev does not describe the use of a therapeutic agent linked to a trivalent Gal/GalNAc asialoglycoprotein receptor targeting moiety. Secondly, the system of Choe is wholly unrelated to the claimed invention. Finally, Guerrab in view of Buckley describes the use of monoclonal antibodies cetuximab or panitumumab to treat HCC in EGFR-expressing tissues. Applicant reiterates that therapeutic antibodies are not encompassed by the pending claims (Remarks, p69 to p70, para 1-3).

Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive for the reasons as follows.

Applicant's argument (i) is not persuasive because Choe et al. teach a pharmaceutical composition comprising the Fc-binding peptide conjugate pre-mixed with antibody as a pharmaceutically acceptable carrier before injection (p12, Fig 9, legend). The pharmaceutically acceptable carrier as claimed includes an antibody. See MPEP 2144 (IV) "RATIONALE DIFFERENT FROM APPLICANT'S IS PERMISSIBLE".

Applicant's argument (ii) is not persuasive because the rejection is based on a combination of 6 references comprising Khorev et al., Guerrab et al., Buckey et al., Choe et al., evidenced by Zhu et al. and Semple et al. NOT a single reference of Khorev et al. as argued by applicant.

Applicant's argument (iii) is not persuasive because the rejection is based on a combination of 6 references NOT a single reference of Guerrab et al. as argued by applicant. In

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particular, Buckley et al. teach overexpression of epidermal growth factor receptor (EGFR) has been observed in around 40% to 70% of conventional Hepatocellular carcinoma, suggesting an overexpressed epidermal growth factor receptor (EGFR) as a drug target of Hepatocellular carcinoma, not limited to a targeting moiety of an antibody or a tyrosine kinase inhibitor as argued by applicant.

Applicant's argument (iv) is not persuasive because Buckley's teaching of "lack of correlation of EGFR protein expression with CEP 7 polysomy" in gliomas and non-small cell lung carcinomas (p249, col 1, para 2) does not change the fact that overexpression of epidermal growth factor receptor (EGFR) by conventional Hepatocellular carcinoma to motivate one of ordinary skill in the art to design a therapeutic agent for targeted cancer therapy.

Applicant's argument (v) is not persuasive because applicant narrowly interprets Choe's teaching. Choe's Fc binding peptide (Fc-III, DCAWHLGELVWCT-NH₂, Figure 3a) with an unusual high binding affinity towards the Fc-region of IgG for both an engineered IgG antibody or endogenous IgG antibody, not limited to the Fc-region of IgG of an engineered IgG antibody as argued by applicant.

Applicant's argument (vi) is not persuasive because (a) applicant's argument is based on dividing the combined references into individually separated references and arguing the flaws of individual reference artificially created by dividing the combination of cited references and (ii) narrowly interpreting the teaching of a cited reference (e.g., limiting Choe's Fc binding peptide to an engineered antibody) and ignoring MPEP 2123 (I) "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Labs., Inc.* 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989), cert. denied, 493 U.S. 975 (1989)."

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For at least the reasons above, the arguments are not persuasive.

Modified Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory

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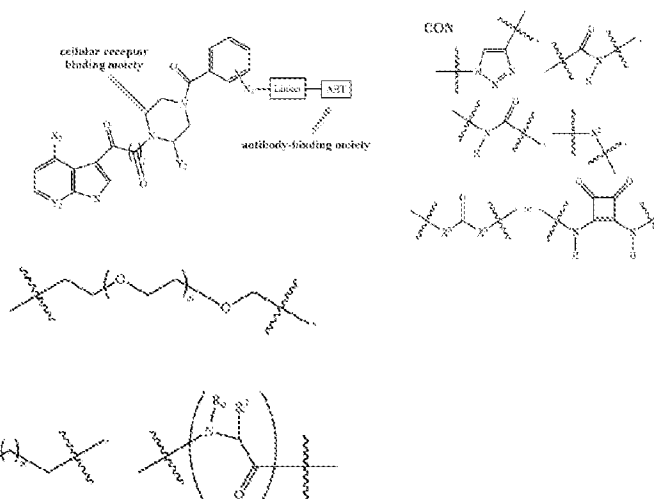
double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

1. Claims 1-2, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 6, and 12 of U.S. Patent No. 9,181,224 (the '224 patent) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).

Claim 1 of the '224 patent disclosed a bifunctional compound, comprising an ABT moiety identical to the instant IgGBM (a)- (c) and a linker optionally comprising a connector moiety shown above.

Claim 6 of the '224 patent disclosed the linker as follows.



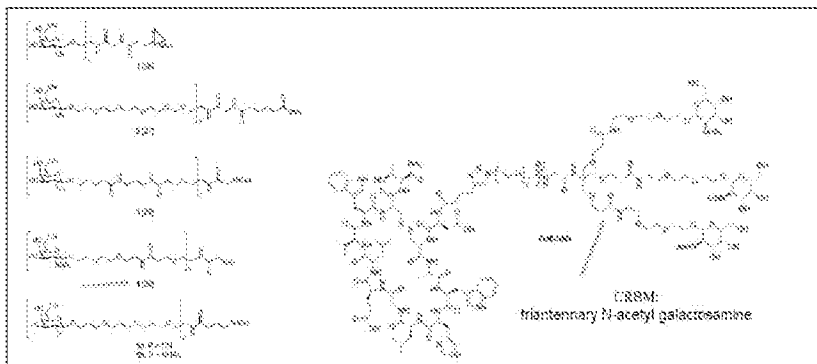
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Claims 1 and 6 of the '224 patent do not teach a cellular receptor binding moiety as a trivalent asialoglycoprotein receptor targeting moiety as claimed.

Khorev et al. teach "Trivalent, Gal/GalNAc-containing ligands designed for the asialoglycoprotein receptor" (Title). Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2).

Khorev et al. teach triantennary ligands displayed a higher affinity than their mono- and



diantennary counterparts. Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2), suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG) and/or amide bond do not significantly affect the terminal galactose and N-acetylgalactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claim 1 of the '224 patent with Khorev's trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Thus, claims 1 and 6 of the '224 patent in view of Khorev et al. is obvious to the instant claims 1-2, and 20-22.

Claim 12 of the '224 patent disclosed a pharmaceutical composition comprising the

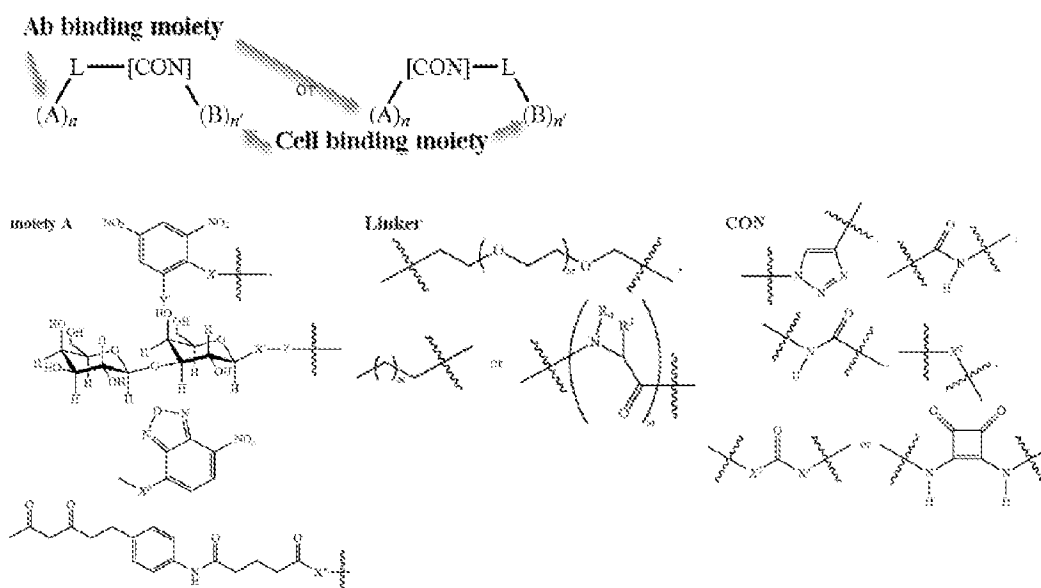
excipient, satisfying the instant claim 27.

Response to Arguments

persuasive because the argument is not applied to the modified rejection.

2. Claims 1-2, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 20 of U.S. Patent No. 9,296,708 (the ‘708 patent) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).

Claim 1 of the '708 patent disclosed a bifunctional compound structure as follows.



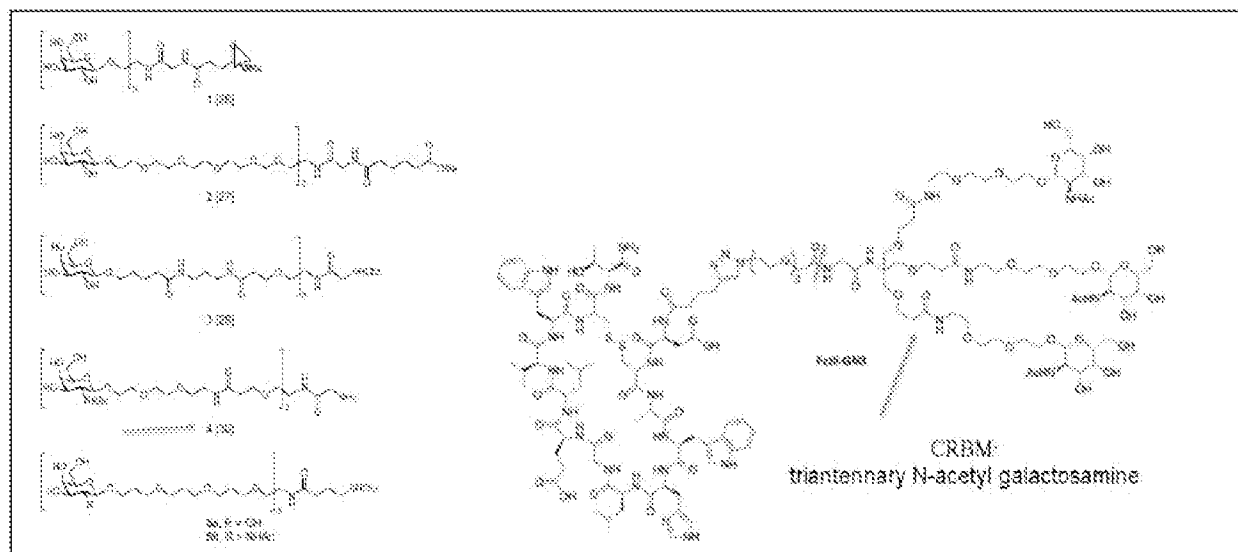
asialoglycoprotein receptor targeting moiety as claimed.

Khorev et al. teach “Trivalent, Gal/GalNAc-containing ligands designed for the asialoglycoprotein receptor” (Title). Khorev et al. show triantennary ligands targeted to ASGP-R.

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as follows (p5218, Fig 2). Khorev et al. teach triantennary ligands displayed a higher affinity



than their mono- and diantennary counterparts. Khorev et al. show triantennary ligands targeted to ASGP-R (p5218, Fig 2), suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG) and/or amide bond do not significantly affect the terminal galactose and N-acetylgalactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claim 1 of the '708 patent with Khorev's trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Thus, claims 1 of the '708 patent in view of Khorev et al. is obvious to the instant claims 1-2 and 20-22.

Claim 20 of the '708 patent disclosed a pharmaceutical composition comprising the bifunctional compound and a pharmaceutically acceptable carrier, additive or excipient,

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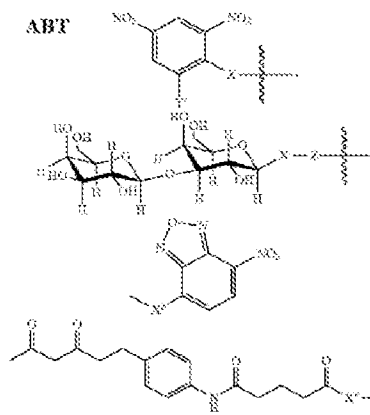
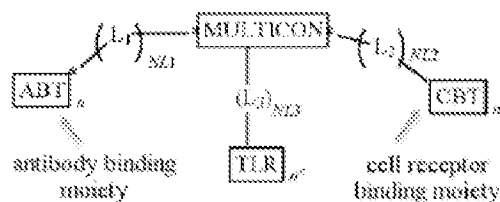
satisfying the instant claim 27.

Response to Arguments

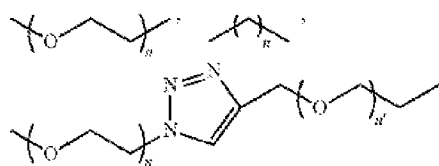
Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument is not applied to the modified rejection.

3. Claims 1-2, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-2, 14 and 26 of U.S. Patent No. 9,556,167 (the '167 patent) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).

Claim 1 of the '167 patent disclosed a bifunctional compound comprising an antibody binding moiety (ABT) and a cell receptor binding moiety as follows. The disclosed ABT moieties read on CPBM in the instant claim 1.



Claim 2 of the '167 patent disclosed the linker comprising the compounds as follows, reading on the CON and linker in the instant claim 1.



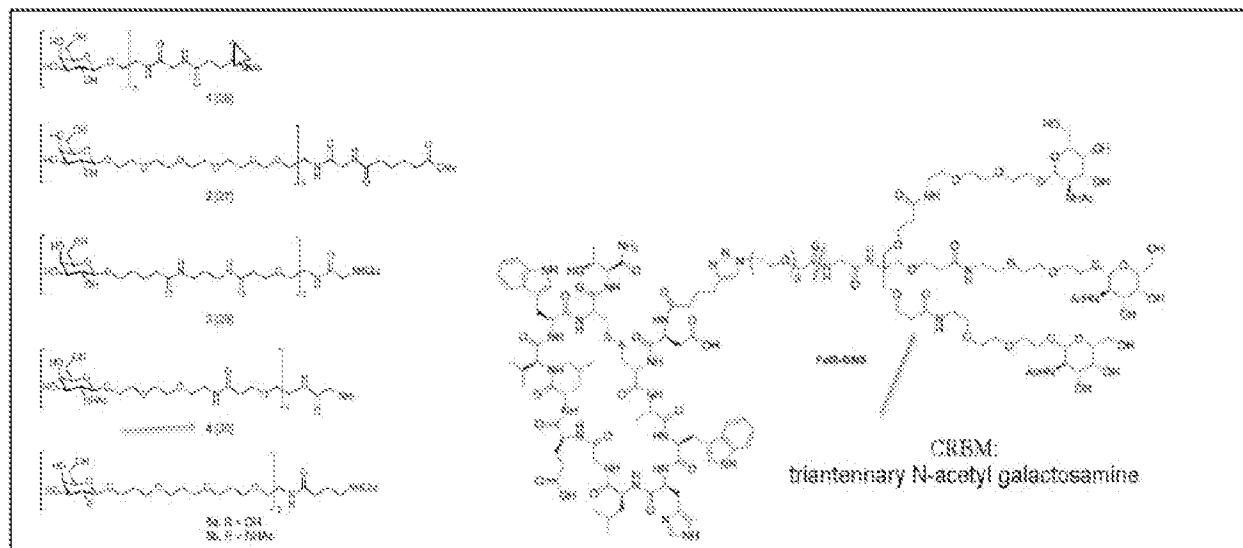
Claims 1-2 of the '167 patent do not teach a cellular receptor binding moiety as a trivalent asialoglycoprotein receptor targeting moiety as claimed.

Khorev et al. teach “Trivalent, Gal/GalNAc-containing ligands designed for the

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asialoglycoprotein receptor" (Title). Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2). Khorev et al. teach triantennary ligands displayed a higher affinity



than their mono- and diantennary counterparts. Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2), suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG) and/or amide bond do not significantly affect the terminal galactose and N-acetylgalactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claim 1 of the '167 patent with Khorev's trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Thus, claims 1-2 of the '167 patent in view of Khorev et al. is obvious to the instant claims 1-2, and 20-22.

Claim 14 of the '167 patent disclosed the linker structures, further satisfying the instant

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claims 20-21.

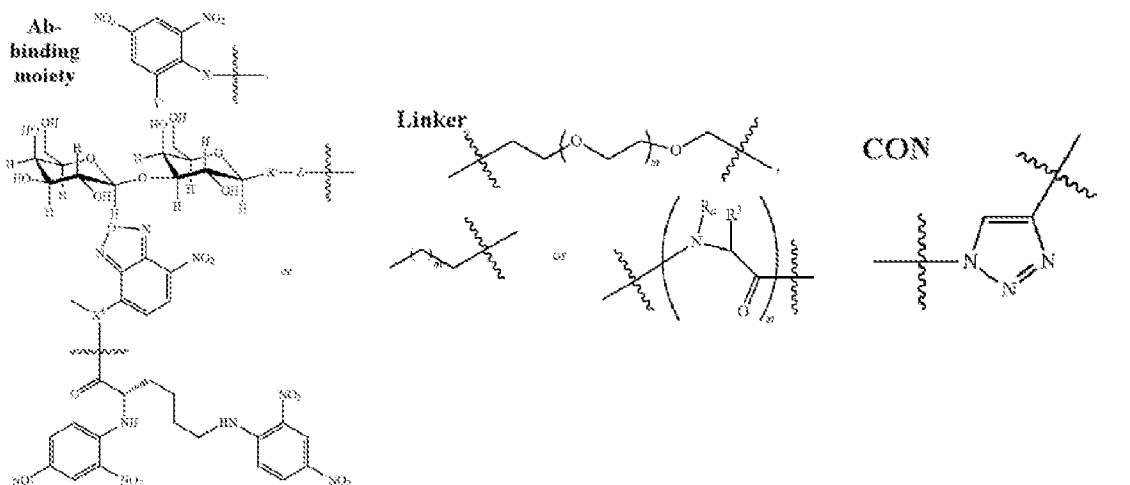
Claim 26 of the '167 patent disclosed a pharmaceutical composition comprising the bifunctional compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument is not applied to the modified rejection.

4. Claims 1-2, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-2, 14, and 21 of U.S. Patent No. 10,066,026 (the '026 patent) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).

Claim 1 of the '026 patent disclosed a bifunctional compound comprising an antibody binding moiety A and a cell receptor binding moiety B as follows.

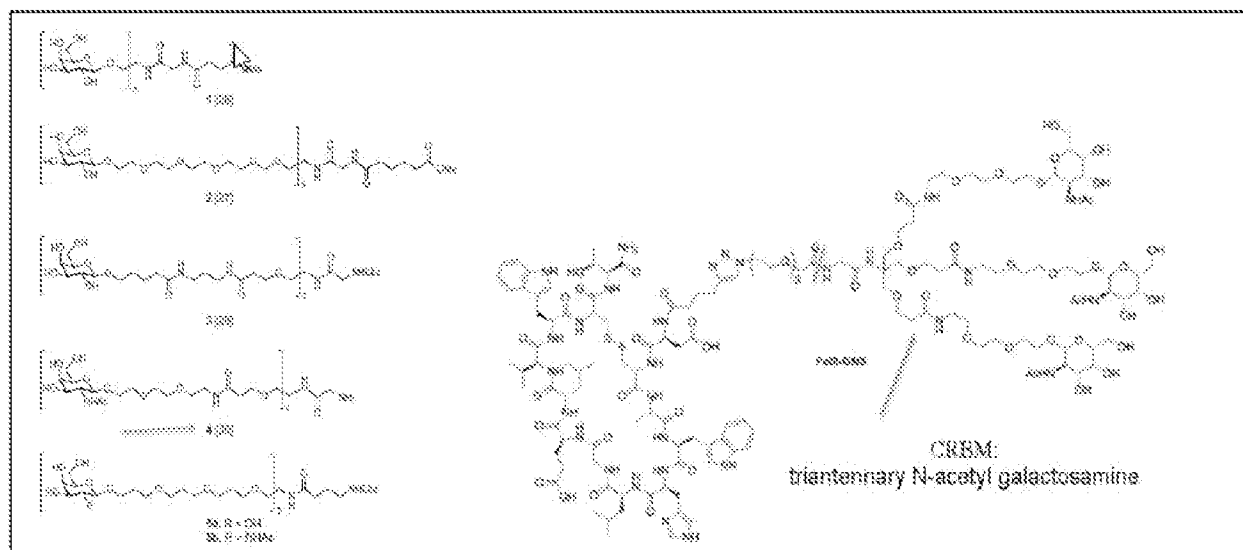


Claim 1 of the '026 patent does not teach a cellular receptor binding moiety as a trivalent asialoglycoprotein receptor targeting moiety as claimed.

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Khorev et al. teach “Trivalent, Gal/GalNAc-containing ligands designed for the asialoglycoprotein receptor” (Title). Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2). Khorev et al. teach triantennary ligands displayed a higher affinity



than their mono- and diantennary counterparts. Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2), suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG) and/or amide bond do not significantly affect the terminal galactose and N-acetylgalactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claim 1 of the ‘167 patent with Khorev’s trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Thus, claim 1 of the ‘026 patent in view of Khorev et al. is

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obvious to the instant claims 1-2, 20-22, and 27.

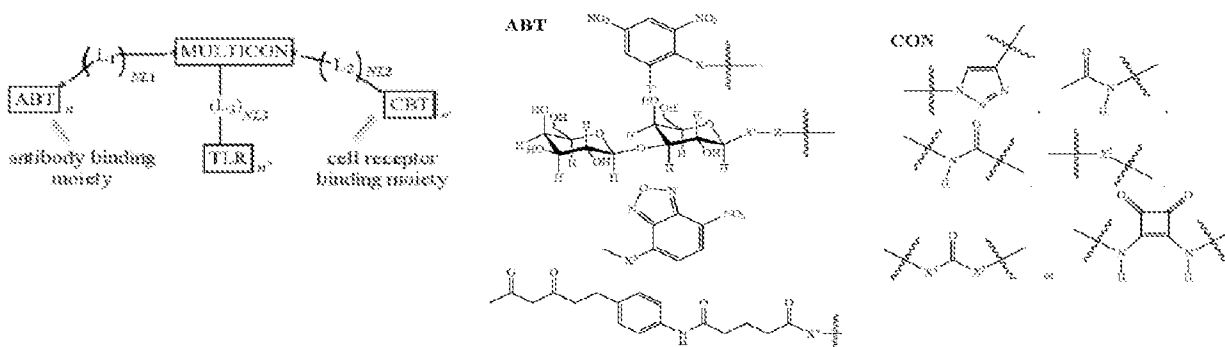
Claim 21 of the '026 patent disclosed a pharmaceutical composition comprising the bifunctional compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Response to Arguments

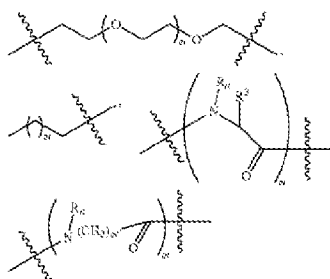
Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument is not applied to the modified rejection.

5. Claims 1-2, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-2, 14, and 23 of U.S. Patent No. 10,016,412 (the '412 patent) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).

Claim 1 of the '412 patent disclosed a bifunctional compound comprising an antibody binding moiety (ABT) and a cell receptor binding moiety as follows. The disclosed ABT moieties read on CPBM in the instant claim 1.



Claim 14 of the '412 patent disclosed the linker structure as follows.

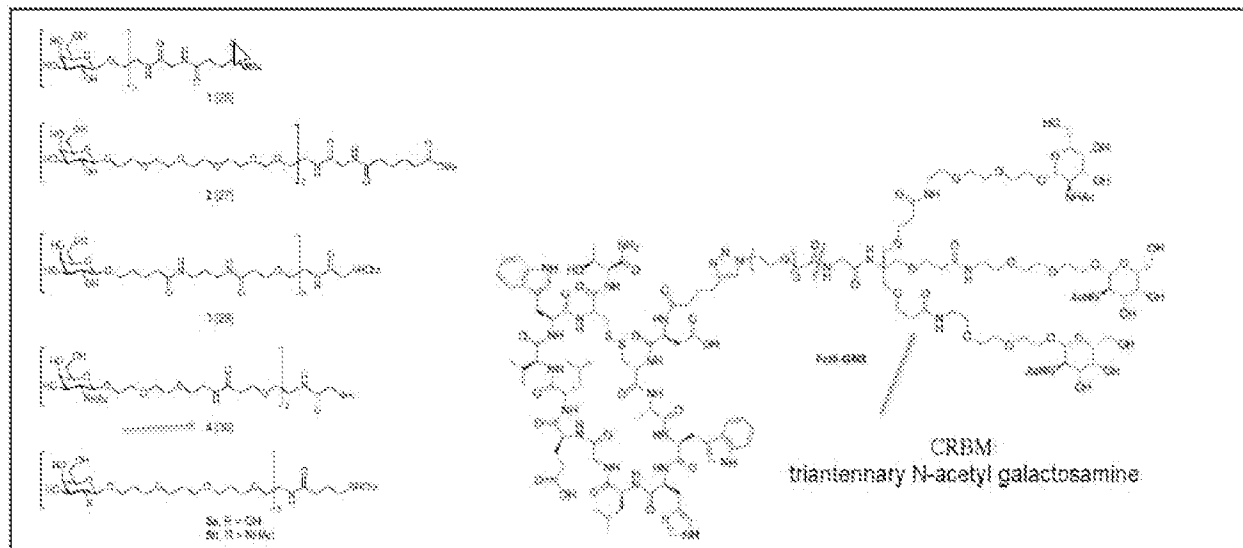


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Claims 1 and 14 of the '412 patent do not disclosed a cellular receptor binding moiety as a trivalent asialoglycoprotein receptor targeting moiety as claimed.

Khorev et al. teach "Trivalent, Gal/GalNAc-containing ligands designed for the



asialoglycoprotein receptor" (Title). Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2). Khorev et al. teach triantennary ligands displayed a higher affinity than their mono- and diantennary counterparts. Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2), suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG) and/or amide bond do not significantly affect the terminal galactose and N-acetyl galactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claim 1 of the '167 patent with Khorev's trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to

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the liver (p5222, col 2, para 1). Thus, claims 1 and 14 of the '412 patent in view of Khorev et al. is obvious to the instant claims 1-2 and 20-22.

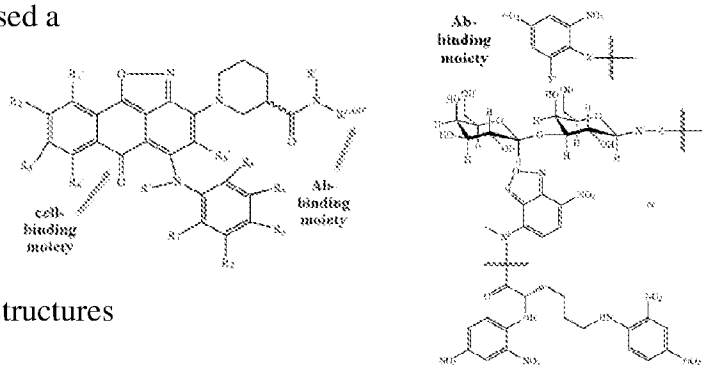
Claim 23 of the '412 patent disclosed a pharmaceutical composition comprising the bifunctional compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Response to Arguments

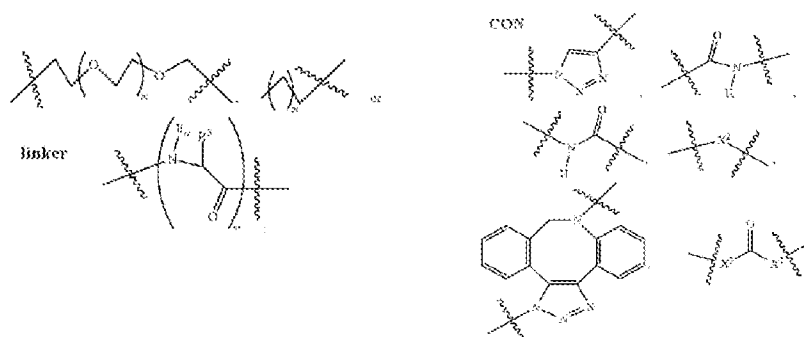
Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument is not applied to the modified rejection.

6. Claims 1-2, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 10, and 31 of U.S. Patent No. 10,633,374 (the '374 patent) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).

Claims 1 of the '374 patent disclosed a bifunctional compound comprising an antibody binding moiety and cell binding moiety as follows. Claim 1 of the '374 patent further disclosed various structures of the antibody binding moiety as follows.



Claim 10 of the '374 patent disclosed linker and CON structures as follows.

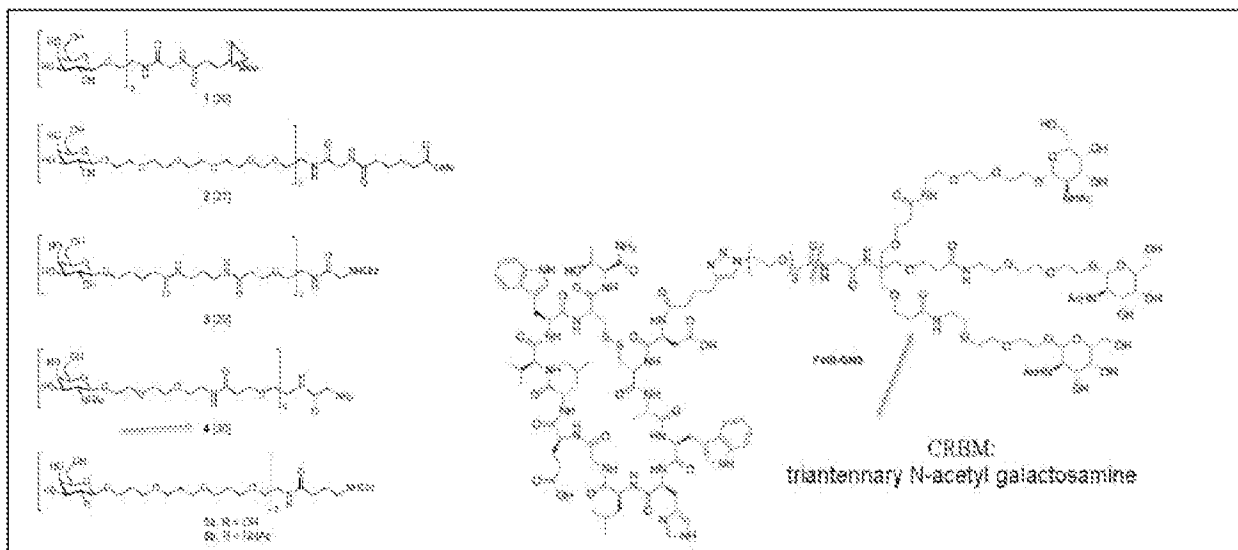


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Claims 1 and 10 of the '374 patent do not disclosed a cellular receptor binding moiety as a trivalent asialoglycoprotein receptor targeting moiety as claimed.

Khorev et al. teach "Trivalent, Gal/GalNAc-containing ligands designed for the asialoglycoprotein receptor" (Title). Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2). Khorev et al. teach triantennary ligands displayed a higher affinity than their mono- and diantennary counterparts. Khorev et al. show triantennary ligands targeted



to ASGP-R as follows (p5218, Fig 2), suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG) and/or amide bond do not significantly affect the terminal galactose and N-acetyl galactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claims 1 and 10 of the '374 patent with Khorev's trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic

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agents to the liver (p5222, col 2, para 1). Thus, claims 1 and 10 of the '374 patent in view of Khorev et al. is obvious to the instant claims 1-2 and 20-22.

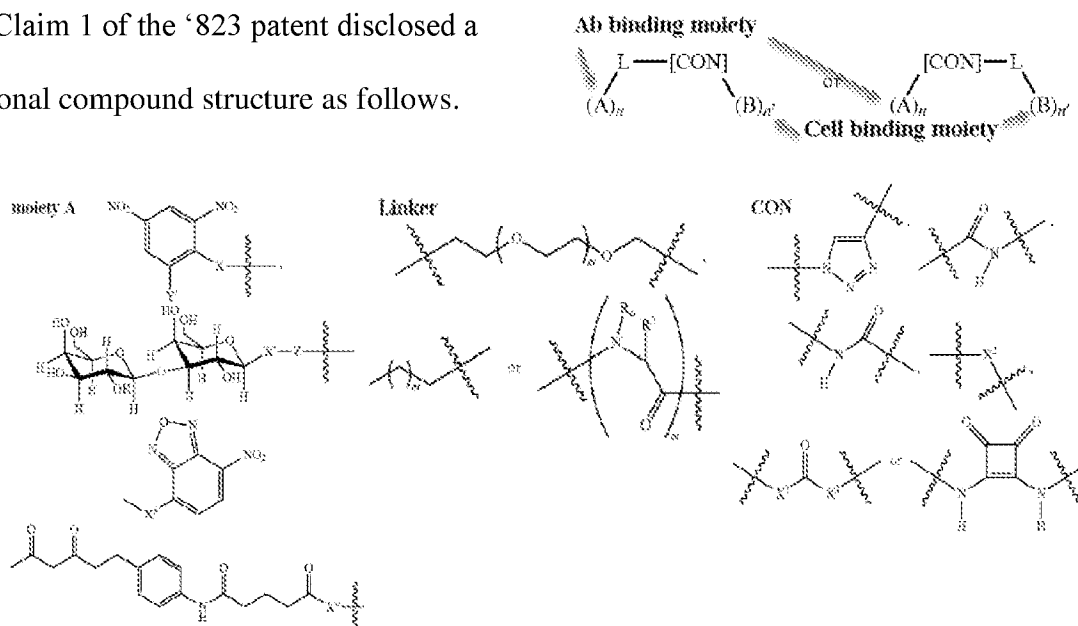
Claim 31 of the '374 patent disclosed a pharmaceutical composition comprising the bifunctional compound and a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument is not applied to the modified rejection.

7. Claims 1-2, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 19 of U.S. Patent No. 10,703,823 (the '823 patent) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).

Claim 1 of the '823 patent disclosed a bifunctional compound structure as follows.



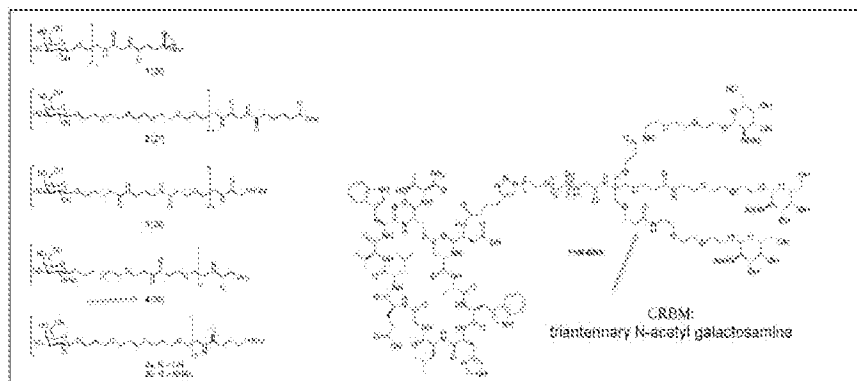
Claim 1 of the '823 patent does not teach a cellular receptor binding moiety as a trivalent asialoglycoprotein receptor targeting moiety as claimed.

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Khorev et al. teach “Trivalent, Gal/GalNAc-containing ligands designed for the asialoglycoprotein receptor” (Title). Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2). Khorev et al. teach triantennary ligands displayed a higher affinity than their mono- and diantennary counterparts. Khorev et al. show triantennary ligands targeted to ASGP-R (p5218, Fig

2), suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG)



and/or amide bond do not significantly affect the terminal galactose and N-acetylgalactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claim 1 of the ‘708 patent with Khorev’s trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Thus, claims 1 of the ‘823 patent in view of Khorev et al. is obvious to the instant claims 1-2 and 20-22.

Claim 19 of the ‘823 patent disclosed a pharmaceutical composition comprising the bifunctional compound and a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

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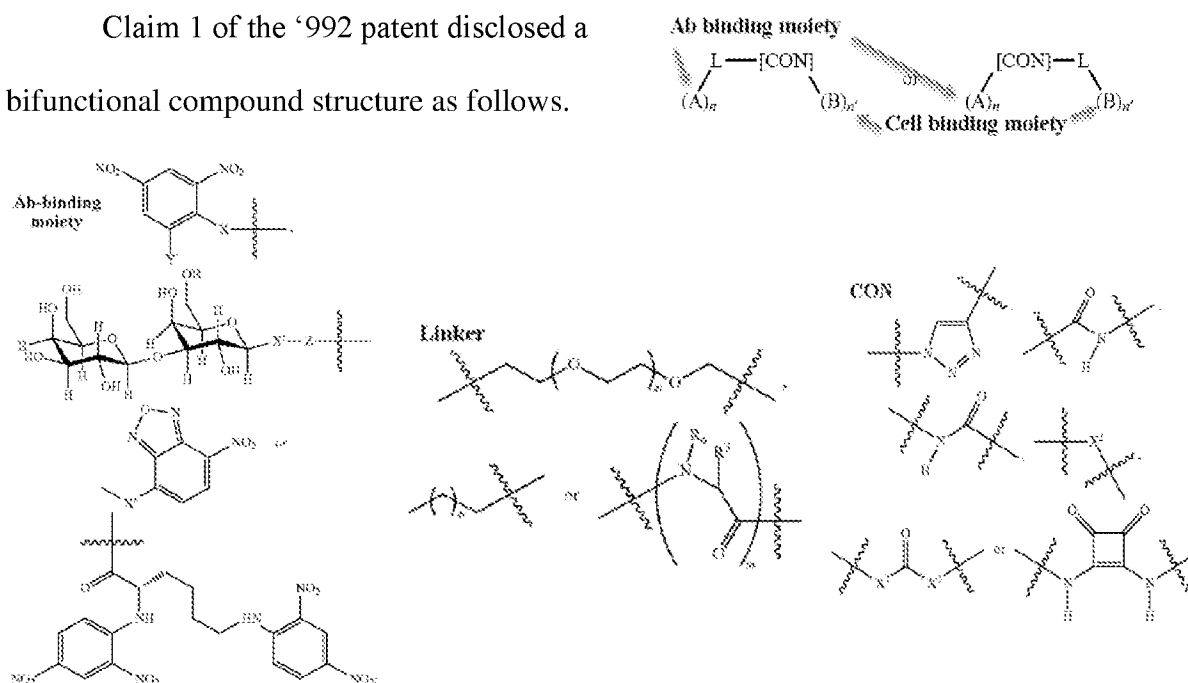
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Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument is not applied to the modified rejection.

8. Claims 1-2, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 16 of U.S. Patent No. 11,014,992 (the '992 patent) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).

Claim 1 of the '992 patent disclosed a bifunctional compound structure as follows.



Claim 1 of the '992 patent does not teach a cellular receptor binding moiety as a trivalent asialoglycoprotein receptor targeting moiety as claimed.

Khorev et al. teach “Trivalent, Gal/GalNAc-containing ligands designed for the asialoglycoprotein receptor” (Title). Khorev et al. show triantennary ligands targeted to ASGP-R (p5218, Fig 2). Khorev et al. teach triantennary ligands displayed a higher affinity than their mono- and diantennary counterparts. Khorev et al. show triantennary ligands targeted to ASGP-R (p5218, Fig 2), suggesting that the linking spacer comprising an alkyl chain

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substituted with oxygen (e.g., PEG) and/or amide bond do not significantly affect the terminal galactose and N-acetylgalactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claim 1 of the '708 patent with Khorev's trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Thus, claims 1 of the '992 patent in view of Khorev et al. is obvious to the instant claims 1-2 and 20-22.

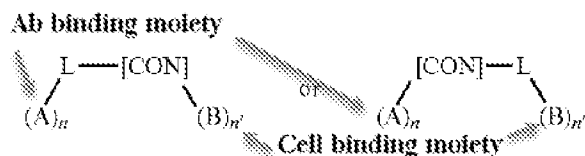
Claim 16 of the '992 patent disclosed a pharmaceutical composition comprising the bifunctional compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument is not applied to the modified rejection.

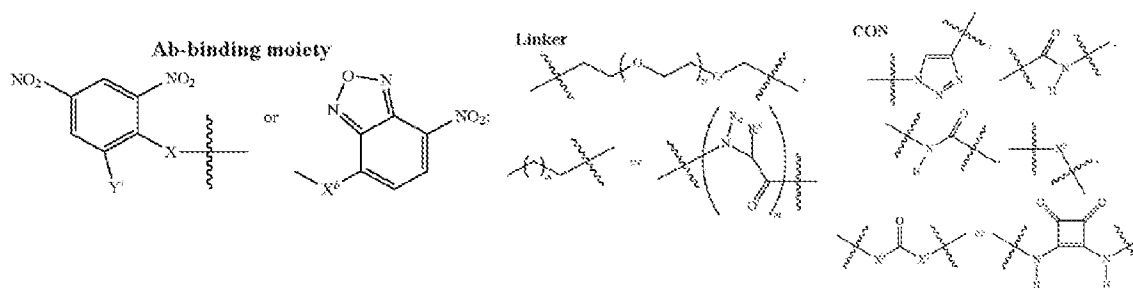
9. Claims 1-2, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 11 of U.S. Patent No. 11,725,064 (the '064 patent) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).

Claim 1 of the '064 patent disclosed a bifunctional compound structure as follows.



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Claim 1 of the '064 patent does not teach a cellular receptor binding moiety as a trivalent asialoglycoprotein receptor targeting moiety as claimed.

Khorev et al. teach "Trivalent, Gal/GalNAc-containing ligands designed for the asialoglycoprotein receptor" (Title). Khorev et al. show triantennary ligands targeted to ASGP-R (p5218, Fig 2). Khorev et al. teach triantennary ligands displayed a higher affinity than their mono- and diantennary counterparts. Khorev et al. show triantennary ligands targeted to ASGP-R (p5218, Fig 2), suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG) and/or amide bond do not significantly affect the terminal galactose and N-acetylgalactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claim 1 of the '064 patent with Khorev's trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Thus, claims 1 of the '064 patent in view of Khorev et al. is obvious to the instant claims 1-2 and 20-22.

Claim 11 of the '064 patent disclosed a pharmaceutical composition comprising the

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bifunctional compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

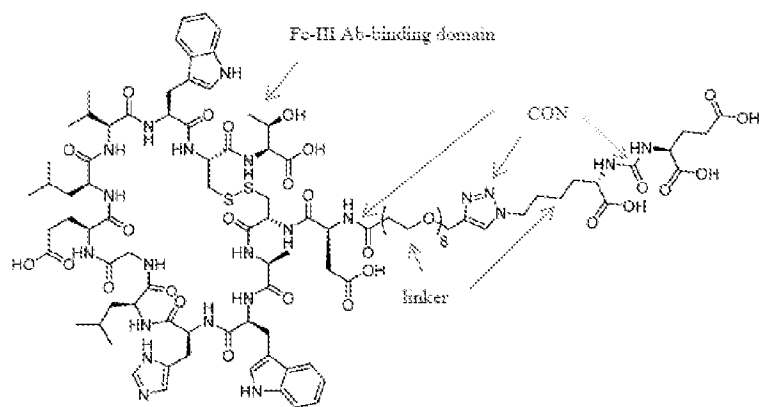
Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument is not applied to the modified rejection.

10. Claims 1-2, 18, 20-22, and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 66, and 83 of copending Application No. 16/634,032 (the '032 application) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).

Claim 1 of the '032 application disclosed a bifunctional compound comprising an antibody binding moiety of Fc-III cyclic peptide and a target binding moiety.

Claim 83 the '032 application disclosed the linker and CON structures for conjugating an antibody binding moiety of Fc-III cyclic peptide to a target binding moiety as follows.



Claims 1 and 83 of the '032 application do not teach a cellular receptor binding moiety as a trivalent asialoglycoprotein receptor targeting moiety as claimed.

Khorev et al. teach “Trivalent, Gal/GalNAc-containing ligands designed for the

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asialoglycoprotein receptor” (Title). Khorev et al. show triantennary ligands targeted to ASGP-R (p5218, Fig 2). Khorev et al. teach triantennary ligands displayed a higher affinity than their mono- and diantennary counterparts. Khorev et al. show triantennary ligands targeted to ASGP-R (p5218, Fig 2), suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG) and/or amide bond do not significantly affect the terminal galactose and N-acetylgalactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claim 1 of the ‘064 patent with Khorev’s trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Thus, claims 1 and 83 of the ‘032 application in view of Khorev et al. is obvious to the instant claims 1-2, 18, and 20-22.

Claim 66 of the ‘032 application disclosed a pharmaceutical composition comprising the bifunctional compound and a pharmaceutically acceptable carrier, adjuvant or vehicle, satisfying the instant claim 27.

This is a provisional nonstatutory double patenting rejection.

Response to Arguments

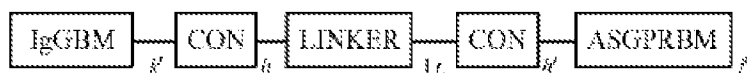
Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument of holding the rejection until allowable subject matter found does not overcome the provisional ODP rejection.

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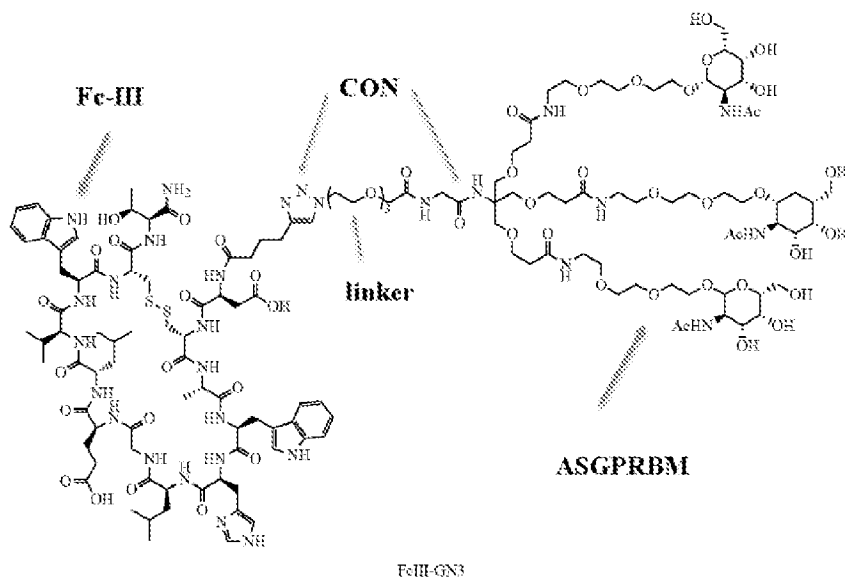
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11. Claims 1-2, 18, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 14 of U.S. Patent No. 11,767,301 (the '301 patent; previously cited as 17/046,192). Although the claims at issue are not identical, they are not patentably distinct from each other because the '301 patent disclosed various compounds obvious to this instant application.

Claim 1 of the '301 patent disclosed a bifunctional compound as follows.



Claim 1 of the '301 patent further disclosed the IgGBM is the elected species of Fc-III with linker and CON structures as follows, satisfying the instant claims 1-2, 18, and 20-22.



Claim 14 of the '301 patent disclosed a pharmaceutical composition comprising the bifunctional compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not

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persuasive because the argument is not applied to the modified rejection.

12. Claims 1-2, 18, 20-22 and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4, 12, 20, 24, 29, and 32 of copending Application No. 17/046,221 (the '221 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '221 application disclosed the elected compound species.

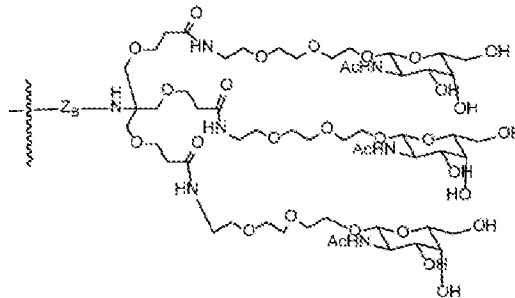
Claim 1 of the '221 application disclosed a bifunctional compound as follows.



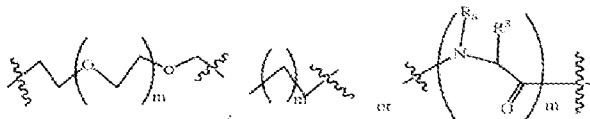
Claims 1 and 20 of the '221 application disclosed a CPBM moiety is the elected species of Fc-III.

Claims 1 and 20 of the '221 application disclosed CPBM moiety is the elected species of Fc-III.

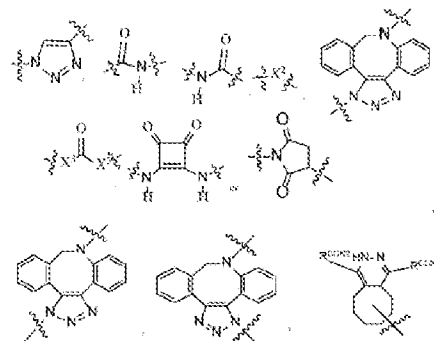
Claims 4 and 12 of the '221 application disclosed CRBM is [ASGPRBM] shown as follows.



Claim 24 of the '221 application disclosed a linker structure as follows.



Claim 29 of the '221 application disclosed CON structures as follows.



Thus, claims 1, 4, 12, 20, 24, and 29 of the '221 application are obvious to the instant

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claims 1-2, 18, and 20-22.

Claim 32 of the '221 application disclosed a pharmaceutical composition comprising the bifunctional compound and a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

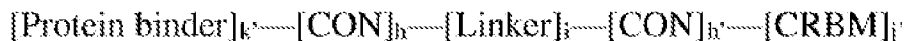
This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Response to Arguments

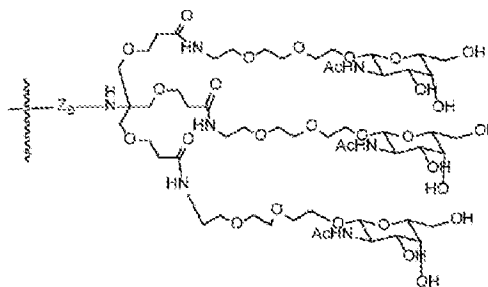
Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument of holding the rejection until allowable subject matter found does not overcome the provisional ODP rejection.

13. Claims 1-2, 18, 20-22 and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 16, 20-21, 23, and 30 of copending Application No. 17/654,990 (the '990 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '990 application disclosed the elected compound species.

Claim 1 of the '990 application disclosed a bifunctional compound as follows.



Claims 16 and 20 of the '990 application disclosed CRBM is [ASGPRBM] shown as follows.

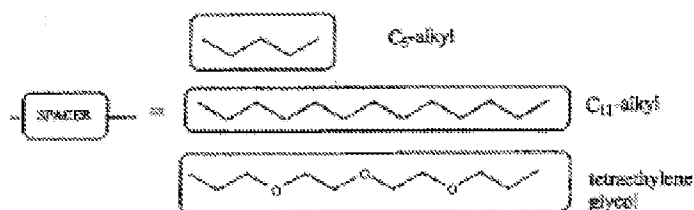


Claims 20-21 of the '990 application disclosed linker structures comprising alkyl or PEG

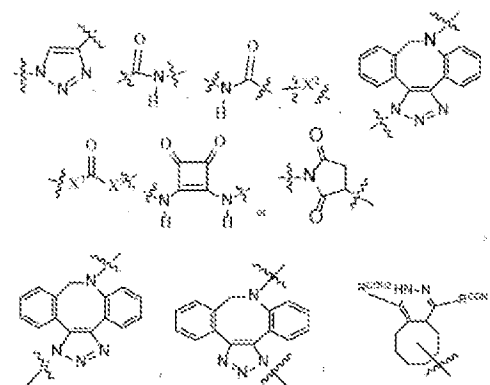
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structure as follows.



Claim 23 disclosed CON structures as follows.



Thus, claims 1, 16, 20-21, and 23 of the '990 application are obvious to the instant claims 1-2, 18, and 20-22.

Claim 30 of the '990 application disclosed a pharmaceutical composition comprising the bifunctional compound and a pharmaceutically acceptable excipient, satisfying the instant claim 27.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument of holding the rejection until allowable subject matter found does not overcome the provisional ODP rejection.

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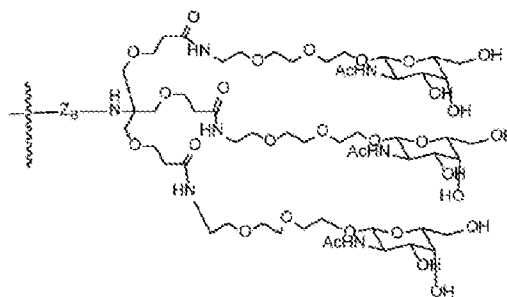
14. Claims 1-2, 18, 20-22 and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3, 10, 18, 21 and 26 of copending Application No. 17/695,259 (the '259 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '259 application disclosed the elected compound species.

Claim 1 of the '259 application disclosed a bifunctional compound as follows.

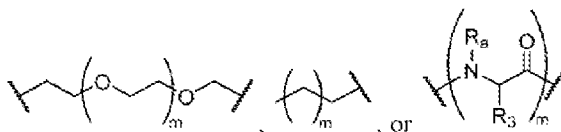


Claim 3 of the '259 application disclosed the protein binder is the elected species Fc-III

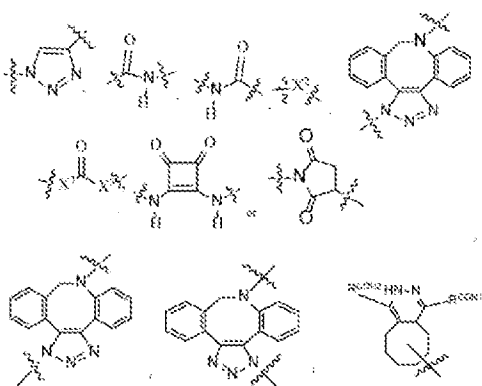
Claim 10 of the '259 application disclosed the CRBM is the elected species of [ASGPRBM] shown as follows.



Claim 18 of the '259 application disclosed the linker structure as follows.



Claim 21 of the '259 application disclosed CON structures as follows.



Thus, claims 1, 3, 10, 18, and 21 of the '259 application are obvious to the instant claims 1-2, 18,

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and 20-22.

Claim 26 of the '259 application disclosed a pharmaceutical composition comprising the bifunctional compound in combination with a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument of holding the rejection until allowable subject matter found does not overcome the provisional ODP rejection.

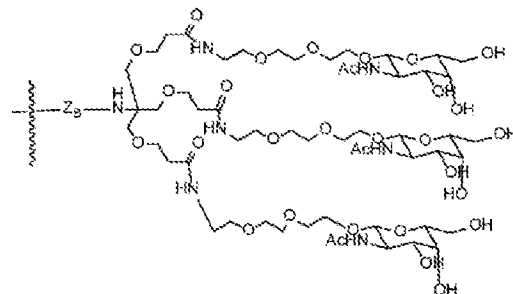
15. Claims 1-2, 18, 20-22 and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3, 10, 17, 21-22 and 26 of copending Application No. 17/695,645 (the '645 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '645 application disclosed the elected compound species.

Claim 1 of the '645 application disclosed a bifunctional compound as follows.



Claims 3 and 17 of the '645 application disclosed the protein binder a the elected species of Fc-III.

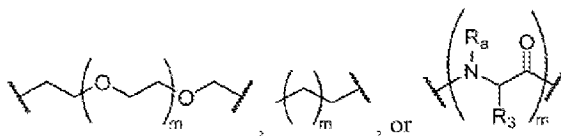
Claim 10 of the '633 application disclosed the CRBM is the elected species of [ASGPRBM] shown as follows.



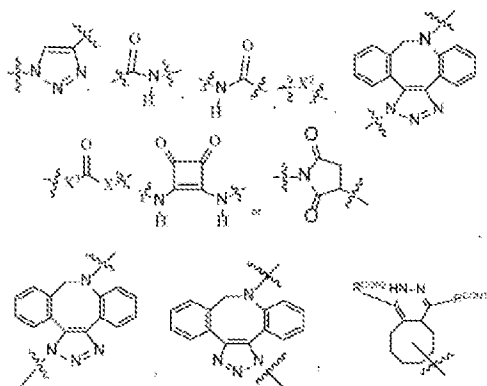
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Claim 21 of the '645 application disclosed the linker structure as follows.



Claim 22 of the '645 application disclosed CON structures as follows.



Thus, claims 1, 3, 10, 17, and 21-22 of the '645 application are obvious to the instant claims 1-2, 18, and 20-22.

Claim 26 of the '645 application disclosed a pharmaceutical composition comprising the bifunctional compound and a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument of holding the rejection until allowable subject matter found does not overcome the provisional ODP rejection.

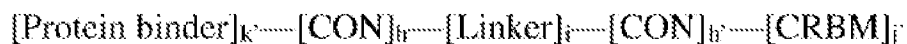
16. Claims 1-2, 18, 20-22 and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 10, 19-22 and 28 of copending Application

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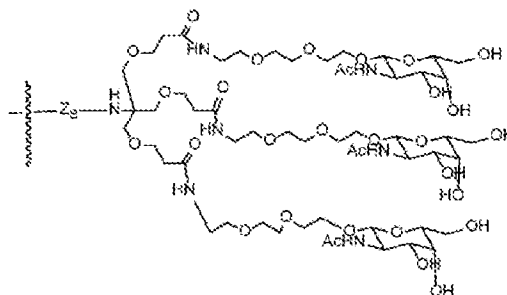
No. 18/161,633 (the '633 application). Although the claims at issue are not identical, they are not patentably distinct from each other because the '633 application disclosed the elected compound species.

Claim 1 of the '633 application disclosed a bifunctional compound as follows.

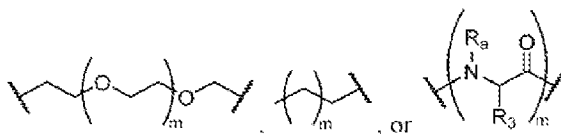


Claim 1 of the '633 application disclosed the protein binder is the elected species of Fc-III.

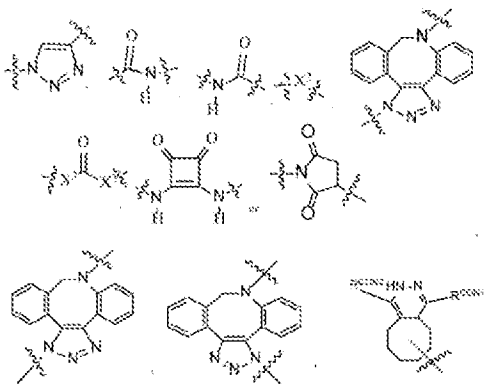
Claim 10 of the '633 application disclosed the CRBM is the elected species of [ASGPRBM] shown as follows.



Claims 1 and 19-21 of the '633 application disclosed the linker structure as follows.



Claims 1 and 22 of the '633 application disclosed CON structures as follows.



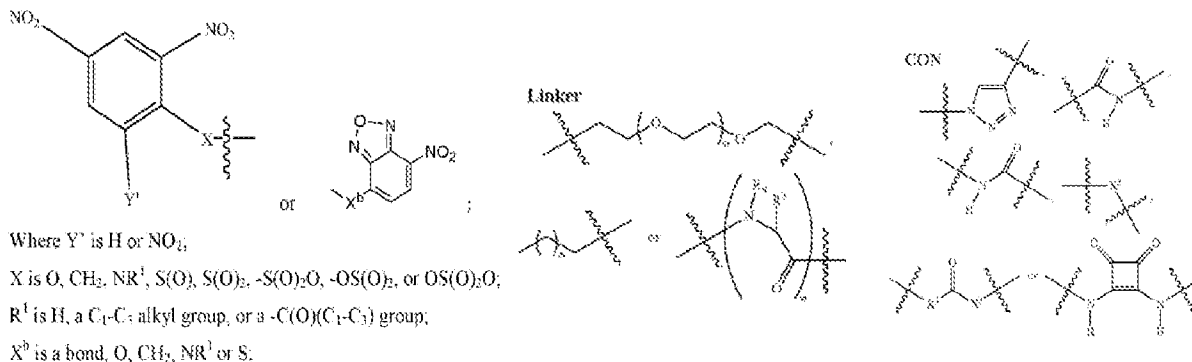
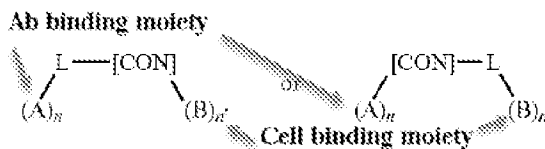
Thus, claims 1, 10, and 19-22 of the '633 application are obvious to the instant claims 1-2, 18, and 20-22.

Claim 28 of the '633 application disclosed a pharmaceutical composition comprising the

bifunctional compound and a pharmaceutically acceptable carrier, additive or excipient, satisfying the instant claim 27.

Response to Arguments

17. Claims 1-2, 20-22, and 27 are rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 18/206,937 (the '937 application) in view of Khorev et al. (Bioorganic & Medicinal Chemistry 16 (2008) 5216–5231.).



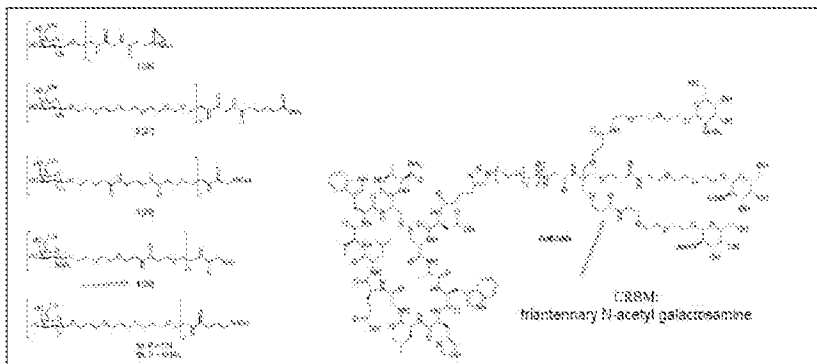
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Claim 1 the '937 application do not teach a cellular receptor binding moiety as a trivalent asialoglycoprotein receptor targeting moiety as claimed.

Khorev et al. teach "Trivalent, Gal/GalNAc-containing ligands designed for the asialoglycoprotein receptor" (Title). Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2).

Khorev et al. teach
triantennary ligands displayed
a higher affinity
than their mono- and



diantennary counterparts. Khorev et al. show triantennary ligands targeted to ASGP-R as follows (p5218, Fig 2), suggesting that the linking spacer comprising an alkyl chain substituted with oxygen (e.g., PEG) and/or amide bond do not significantly affect the terminal galactose and N-acetylgalactosamine binding to Asialoglycoprotein receptors of hepatocytes. Khorev et al. further suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Because Khorev et al. suggest the beneficial use of a trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to asialoglycoprotein receptor expressing liver cells (e.g., hepatocellular carcinoma), one of ordinary skill in the art would have found it obvious to substitute the cellular receptor binding moiety disclosed by claim 1 of the '937 application with Khorev's trivalent Gal/GalNAc targeting ligand for site-specific delivery of therapeutic agents to the liver (p5222, col 2, para 1). Thus, claim 1 of the '937 application in view of Khorev et al. is obvious to the instant claims 1-2, 20-22, and 27.

This is a provisional nonstatutory double patenting rejection because the patentably

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indistinct claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed 12/11/2023 have been fully considered but they are not persuasive because the argument of holding the rejection until allowable subject matter found does not overcome the provisional ODP rejection.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JIA-HAI LEE whose telephone number is (571)270-1691. The examiner can normally be reached Mon-Fri from 9:00 AM to 6:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using

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a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melissa Fisher can be reached on 571-270-7430. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1658

/ARADHANA SASAN/
Primary Examiner, Art Unit 1615

05-January-2024

EXHIBIT 18

From: Lopez, Jovan [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3B24969D7CD14D01BDC0EDB70B5305F7-JAL323]
Sent: 5/4/2023 11:25:30 AM
To: Mcdonald, David [david.mcdonald@yale.edu]
Subject: [REDACTED]

Hi David,

Could you try sending the attachment again? I couldn't see it on my end.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

All my best,
Jovan

From: Mcdonald, David <david.mcdonald@yale.edu>
Sent: Wednesday, May 3, 2023, 21:51
To: Lopez, Jovan <jovan.lopez@yale.edu>
Subject: Measuring CpaA depletion using HiBiT/LgBiT

Hi Jovan,

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Cheers,

David.

EXHIBIT 19

From: Wiesler, William [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=FA3C3C1BE2AC4BBB903185EEF1F8503B-WW84]
Sent: 12/7/2018 4:26:21 PM
To: Iwasaki, Akiko [akiko.iwasaki@yale.edu]; Miranker, Andrew [andrew.miranker@yale.edu]; Xiao, Andrew [andrew.xiao@yale.edu]; anna.pyle@yale.edu [anna.pyle@bulldogs.yale.edu]; Van den Pol, Anthony [anthony.vandenpol@yale.edu]; Bennett, Anton [anton.bennett@yale.edu]; Pedroso Balbo, Bruno [bruno.pedrosobalbo@yale.edu]; Fedeles, Sorin [sorin.fedeles@yale.edu]; Somlo, Stefan [stefan.somlo@yale.edu]; Ehrlich, Barbara [barbara.ehrlich@yale.edu]; Ben Mamoun, Choukri [choukri.benmamoun@yale.edu]; Bunick, Christopher [christopher.bunick@yale.edu]; Bergwitz, Clemens [clemens.bergwitz@yale.edu]; Spiegel, David [david.spiegel@yale.edu]; Braddock, Demetrios [demetrios.braddock@yale.edu]; Isaacs, Farren [farren.isaacs@yale.edu]; Rinehart, Jesse [jesse.rinehart@yale.edu]; Eswarakumar, Jacob [jacob.eswarakumar@yale.edu]; Bender, Jeffrey [jeffrey.bender@yale.edu]; Zhou, Jiangbing [jiangbing.zhou@yale.edu]; Deacon, John [john.deacon@yale.edu]; Saltzman, W. Mark [mark.saltzman@yale.edu]; Girardi, Michael [michael.girardi@yale.edu]; Vukmirovic, Milica [milica.vukmirovic@yale.edu]; Kaminski, Naftali [naftali.kaminski@yale.edu]; Sestan, Nenad [nenad.sestan@yale.edu]; Lee, Patty [patty.lee@yale.edu]; Turner, Paul [paul.turner@yale.edu]; Bonde, Pramod [pramod.bonde@yale.edu]; Chen, Sidi [sidi.chen@yale.edu]; Strittmatter, Stephen [stephen.strittmatter@yale.edu]; Kyriakides, Themis [themis.kyriakides@yale.edu]; Mehal, Wajahat [wajahat.mehal@yale.edu]; william.jorgensen@yale.edu [william.jorgensen@bulldogs.yale.edu]; Ha, Ya [ya.ha@yale.edu]; Zhu, Yong [yong.zhu@yale.edu]
CC: Puziss, John [john.puziss@yale.edu]; Lewin, David [david.lewin@yale.edu]; Unsworth, Christopher [christopher.unsworth@yale.edu]; Peng, Hong [hong.peng@yale.edu]; Truax, Valarie [valarie.truax@yale.edu]; Kadiri, Lolahon [lolahon.kadiri@yale.edu]; Andersson, Richard [richard.andersson@yale.edu]; Boyle, James [james.g.boyle@yale.edu]; Schrager, Lori [lori.schrager@yale.edu]; Fedeles, Sorin [sorin.fedeles@yale.edu]; Siegert, Timothy [timothy.siegert@yale.edu]; Rufo, Caroline [caroline.rufo@yale.edu]; Vukmirovic, Milica [milica.vukmirovic@yale.edu]; Opstrup, Tim [timothy.opstrup@yale.edu]; Vance, Julie [julie.vance@yale.edu]; Grassie, Morag [morag.grassie@yale.edu]
Subject: BLAVATNIK SEMIFINALISTS- FULL APPLICATION DEADLINE IS MONDAY, DEC. 10th, 5pm

Dear Blavatnik Semifinalists,

Our deadline to SUBMIT your **ENTIRE BLAVATNIK APPLICATION**, most importantly the updated slides for Pitchfest is **5pm Monday December 10th**. There is a lot of work to do to prepare them all for seamless presentation at Pitchfest. They will be compiled into a single file, and so we **WILL NOT BE ACCOMODATING LAST MINUTE CHANGES**. **DO NOT SHOW UP TO PITCHFEST WITH A THUMBDRIVE ASKING TO CHANGE SLIDES**.

Your Pitchfest decks and videotaped presentations should be **NON-CONFIDENTIAL**. These materials, together with **one or two of your key publications**, will be made available to interested commercial parties on our Blavatnik Portal. Most of you do not require sharing confidential information to make a strong proposal for funding.

OPTIONAL: If you or your OCR lead believe that disclosure of **SUPPLEMENTAL CONFIDENTIAL DATA SLIDES** are absolutely required to present a comprehensible proposal to the Blavatnik Board, then you will be allowed to submit **SUPPLEMENTAL SLIDES**, not to exceed 5 slides. (Note we will not be having you create a complete "confidential deck. Just extra slides if necessary). That data should be presented in a way that is **COMPLETELY SELF-EXPLANATORY** since your video will not include your explanations. Those slides (denoted with the addition of "SUP CONF" to the title) **will also be due at 5pm on Monday December 10th**. This confidential information will be made available to commercial parties that are under CDA, unless you let us know a reason to proceed otherwise. Companies like AbbVie have signed CDAs and are actively hunting for Yale partnering opportunities.

Use this Qualtrics Link to submit your required slide deck and any of the three optional elements (Supplemental Confidential Slides and 2 Publications).

https://yalesurvey.ca1.qualtrics.com/jfe/preview/SV_8jJColsve5qFGdL?Q_SurveyVersionID=current&Q_CHL=preview

IF YOU HAVE TWO APPLICATIONS, YOU NEED TO DO ALL OF THIS TWICE.

Remember, all slide decks need slides on **PATENTS, COMPETITION, and ROUGH BREAKDOWN ON USE OF FUNDS** (guesstimate costs of the 2-4 activities that add up to \$300K).

PITCHFEST NOTES: The material presented at Pitchfest including the video will be reviewed by the Blavatnik board after Pitchfest to select Blavatnik Finalists. No Blavatnik decisions are made at Pitchfest.

However, completely separate from the Blavatnik process, we will have **4 cash prizes** awarded, just to make things fun. They are: Highest Potential Impact \$1000, Most Innovative Breakthrough \$1000, Best Presentation \$1000, and Most Valuable Pitch \$1500.

Your pitch must be delivered in 5 minutes exactly. Out of fairness to your colleagues, a moderator will ask you to stop after 5 minutes. There will be exactly 2 minutes for questions, taking questions from one of our industry judges. We have judges from the very top pharmaceutical companies and biotech venture firms, including Merck, Pfizer, J&J, Polaris Ventures, RA Capital, Accelerator Corp., and Arch Ventures.

Let us know of any questions or concerns you may have at any point between now and Monday's deadline.

Best,

Bill

Bill Wiesler, Ph.D.
Director of New Ventures
Director of the Blavatnik Fund for Innovation at Yale
Office of Cooperative Research
YALE UNIVERSITY
433 Temple Street, First Floor
New Haven, CT 06511
Tel 203.432.5406
Mobile 203.314.4409

EXHIBIT 20

The Provided Natively

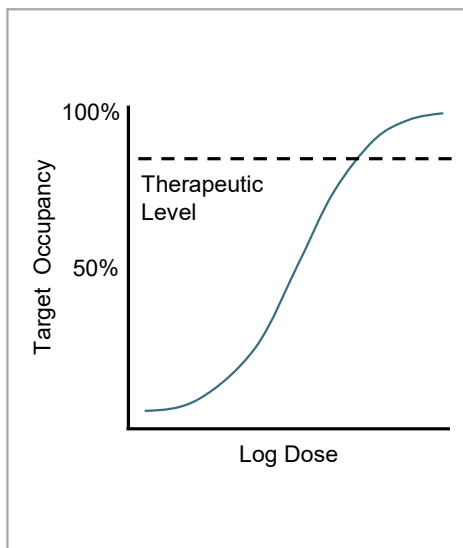
MODA Pharmaceuticals

Targeted Elimination of Pathogenic Extracellular Proteins

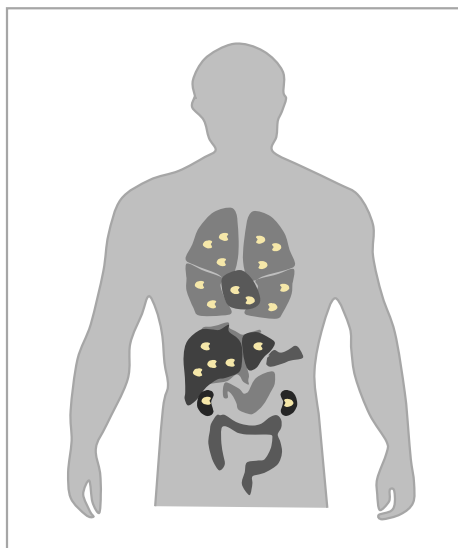
David A. Spiegel, MD, PhD

Yale Lifesciences Pitchfest / December 12, 2018

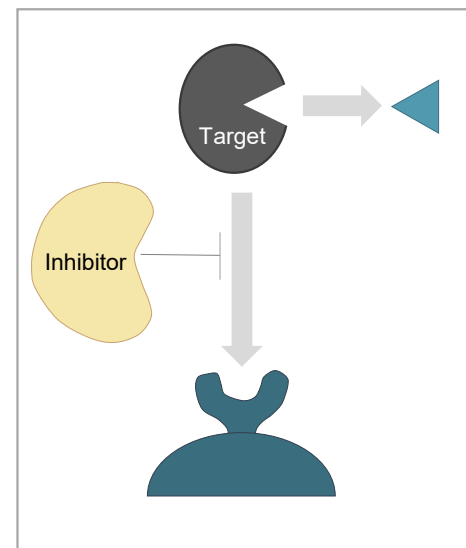
Challenges with Conventional Inhibitors



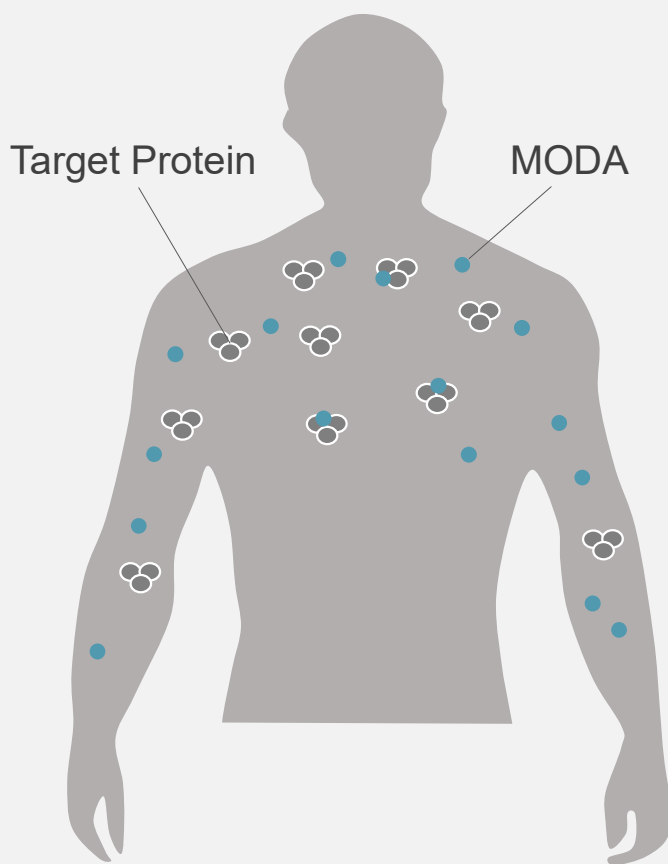
Occupancy of target is required for drug activity, which mandates sustained exposure to drug substance



Toxicity due to requirement of large systemic drug concentrations to ensure sufficient functional inhibition



Only a specific activity of target is controlled and may not result in loss of function of other activities

















Our Approach: The MODA Platform

- MODA Pharmaceuticals is built around a novel technology platform that enables development of **customizable small molecules** for **targeted elimination** of **extracellular proteins**
- MODA small molecules are designed to **bind to extracellular target proteins** and cause them to be **removed from the body**
- Existing targeted small molecule strategies (e.g. Kymera, Arvinas, C4) focus on eliminating **intracellular not extracellular** proteins

KEY FEATURES:

- Extracellular protein targets are eliminated as opposed to inhibited
- MODA therapeutics can be small molecule- or antibody-based
- Small molecule-based design opens up avenues for oral administration
- Potential to reduce drug exposure and off-target effects

Competitive Landscape for Immunoglobulin-Targeting Technologies

	Company	Technology Platform	Technology	Mode of Action
Therapeutics	Hansa Medical	Enzyme	Immunoglobulin G-degrading enzyme of <i>Streptococcus pyogenes</i> (IdeS)	Cleaves human IgG at the hinge region producing F(ab') ₂ and Fc fragments, cleaved IgG is unable to activate complement and promote other pathogenic processes
		Antibody	Efgartigimod- Human IgG1 Fc-fragment designed using ABDEG™ technology	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
		Antibody	SYNT001- Humanized monoclonal antibody engineered to have high affinity for FcRn	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
		Antibody	M281- Fully Human Fab aglycosylated IgG1 monoclonal antibody	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
		Antibody	Rozanolixizumab- a humanized high-affinity anti-human neonatal Fc receptor (FcRn) monoclonal antibody (IgG4P)	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
Plasmapheresis/IVIG	         			

**THE MODA
ADVANTAGE**



MODA Pharmaceuticals

David A. Spiegel, MD, PhD

Email: david.spiegel@yale.edu

Office: 203-432-8697

EXHIBIT 21

From: Spiegel, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0835116661DB416199961B1ECE52169C-DS256]
Sent: 12/10/2018 3:47:31 PM
To: Bhatt, Sumantha [sumantha.bhatt@yale.edu]
Subject: FW: BLAVATNIK SEMIFINALISTS- PowerPoint Only! (No Pdf's)
Attachments: Moda_Yale Lifesciences Pitchfest_2018-12_2.pptx

Would you mind submitting this? Please see final slides attached.

From: "Wiesler, William" <bill.wiesler@yale.edu>

Date: Sunday, December 9, 2018 at 7:19 PM

To: "Iwasaki, Akiko" <akiko.iwasaki@yale.edu>, "Miranker, Andrew" <andrew.miranker@yale.edu>, "Xiao, Andrew" <andrew.xiao@yale.edu>, "anna.pyle@yale.edu" <anna.pyle@bulldogs.yale.edu>, "Van den Pol, Anthony" <anthony.vandenpol@yale.edu>, "Bennett, Anton" <anton.bennett@yale.edu>, "Pedroso Balbo, Bruno" <bruno.pedrosobalbo@yale.edu>, "Fedeles, Sorin" <sorin.fedeles@yale.edu>, "Somlo, Stefan" <stefan.somlo@yale.edu>, "Ehrlich, Barbara" <barbara.ehrlich@yale.edu>, "Ben Mamoun, Choukri" <choukri.benmamoun@yale.edu>, "Bunick, Christopher" <christopher.bunick@yale.edu>, "Bergwitz, Clemens" <clemens.bergwitz@yale.edu>, David Spiegel <david.spiegel@yale.edu>, "Braddock, Demetrios" <demetrios.braddock@yale.edu>, "Isaacs, Farren" <farren.isaacs@yale.edu>, "Rinehart, Jesse" <jesse.rinehart@yale.edu>, "Eswarakumar, Jacob" <jacob.eswarakumar@yale.edu>, "Bender, Jeffrey" <jeffrey.bender@yale.edu>, "Zhou, Jiangbing" <jiangbing.zhou@yale.edu>, "Deacon, John" <john.deacon@yale.edu>, "Saltzman, W. Mark" <mark.saltzman@yale.edu>, "Girardi, Michael" <michael.girardi@yale.edu>, "Vukmirovic, Milica" <milica.vukmirovic@yale.edu>, "Kaminski, Naftali" <naftali.kaminski@yale.edu>, "Sestan, Nenad" <nenad.sestan@yale.edu>, "Lee, Patty" <patty.lee@yale.edu>, "Turner, Paul" <paul.turner@yale.edu>, "Bonde, Pramod" <pramod.bonde@yale.edu>, "Chen, Sidi" <sidi.chen@yale.edu>, "Strittmatter, Stephen" <stephen.strittmatter@yale.edu>, "Kyriakides, Themis" <themis.kyriakides@yale.edu>, "Mehal, Wajahat" <wajahat.mehal@yale.edu>, "william.jorgensen@yale.edu" <william.jorgensen@bulldogs.yale.edu>, "Ha, Ya" <ya.ha@yale.edu>, "Zhu, Yong" <yong.zhu@yale.edu>
Cc: "Puziss, John" <john.puziss@yale.edu>, "Lewin, David" <david.lewin@yale.edu>, "Unsworth, Christopher" <christopher.unsworth@yale.edu>, "Peng, Hong" <hong.peng@yale.edu>, "Truax, Valarie" <valarie.truax@yale.edu>, "Kadiri, Lolahon" <lolahon.kadiri@yale.edu>, "Andersson, Richard" <richard.andersson@yale.edu>, "Boyle, James" <james.g.boyle@yale.edu>, "Schrager, Lori" <lori.schrager@yale.edu>, "Siegert, Timothy" <timothy.siegert@yale.edu>, "Rufo, Caroline" <caroline.rufo@yale.edu>, "Opstrup, Tim" <timothy.opstrup@yale.edu>, "Vance, Julie" <julie.vance@yale.edu>, "Grassie, Morag" <morag.grassie@yale.edu>, "Quaye, Mercy" <mercy.quaye@yale.edu>

Subject: BLAVATNIK SEMIFINALISTS- PowerPoint Only! (No Pdf's)

Please send only PowerPoint slides. (No pdf).

That's the only way we can accommodate video AND merge everyone's slides into a master PitchFest deck.

Thank you!

Sent from my iPhone

On Dec 7, 2018, at 4:26 PM, Wiesler, William <bill.wiesler@yale.edu> wrote:

Dear Blavatnik Semifinalists,

Our deadline to SUBMIT your **ENTIRE BLAVATNIK APPLICATION**, most importantly the updated slides for Pitchfest is **5pm Monday December 10th**. There is a lot of work to do to prepare them all for seamless presentation at Pitchfest. They will be compiled into a single file, and so we WILL NOT BE ACCOMODATING LAST MINUTE CHANGES. DO NOT SHOW UP TO PITCHFEST WITH A THUMBDRIVE ASKING TO CHANGE SLIDES.

Your Pitchfest decks and videotaped presentations should be **NON-CONFIDENTIAL**. These materials, together with **one or two of your key publications**, will be made available to interested commercial parties on our Blavatnik Portal. Most of you do not require sharing confidential information to make a strong proposal for funding.

OPTIONAL: If you or your OCR lead believe that disclosure of **SUPPLEMENTAL CONFIDENTIAL DATA SLIDES** are absolutely required to present a comprehensible proposal to the Blavatnik Board, then you will be allowed to submit SUPPLEMENTAL SLIDES, not to exceed 5 slides. (Note we will not be having you create a complete "confidential deck. Just extra slides if necessary). That data should be presented in a way that is COMPLETELY SELF-EXPLANATORY since your video will not include your explanations. Those slides (denoted with the addition of "SUP CONF" to the title) **will also be due at 5pm on Monday December 10th**. This confidential information will be made available to commercial parties that are under CDA, unless you let us know a reason to proceed otherwise. Companies like AbbVie have signed CDAs and are actively hunting for Yale partnering opportunities.

Use this Qualtrics Link to submit your required slide deck and any of the three optional elements (Supplemental Confidential Slides and 2 Publications).

https://yalesurvey.ca1.qualtrics.com/jfe/preview/SV_8jIColsve5qFGdL?Q_SurveyVersionID=current&Q_CHL=preview

IF YOU HAVE TWO APPLICATIONS, YOU NEED TO DO ALL OF THIS TWICE.

Remember, all slide decks need slides on **PATENTS, COMPETITION, and ROUGH BREAKDOWN ON USE OF FUNDS** (guesstimate costs of the 2-4 activities that add up to \$300K).

PITCHFEST NOTES: The material presented at Pitchfest including the video will be reviewed by the Blavatnik board after Pitchfest to select Blavatnik Finalists. No Blavatnik decisions are made at Pitchfest.

However, completely separate from the Blavatnik process, we will have **4 cash prizes** awarded, just to make things fun. They are: Highest Potential Impact \$1000, Most Innovative Breakthrough \$1000, Best Presentation \$1000, and Most Valuable Pitch \$1500.

Your pitch must be delivered in 5 minutes exactly. Out of fairness to your colleagues, a moderator will ask you to stop after 5 minutes. There will be exactly 2 minutes for questions, taking questions from one of our industry judges. We have judges from the very top pharmaceutical companies and biotech venture firms, including Merck, Pfizer, J&J, Polaris Ventures, RA Capital, Accelerator Corp., and Arch Ventures.

Let us know of any questions or concerns you may have at any point between now and Monday's deadline.

Best,

Bill

Bill Wiesler, Ph.D.

Director of New Ventures

Director of the Blavatnik Fund for Innovation at Yale

Office of Cooperative Research

YALE UNIVERSITY

433 Temple Street, First Floor
New Haven, CT 06511
Tel 203.432.5406
Mobile 203.314.4409

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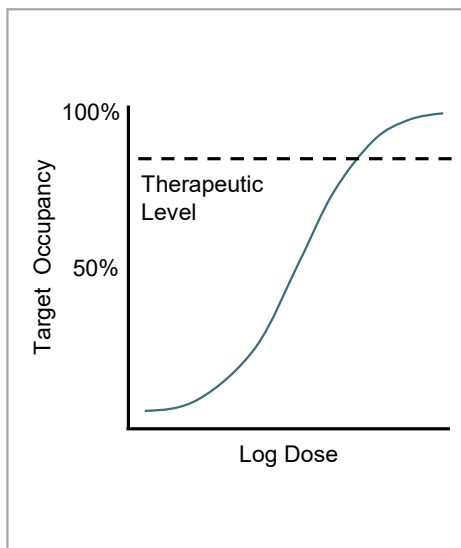
MODA Pharmaceuticals

Targeted Elimination of Pathogenic Extracellular Proteins

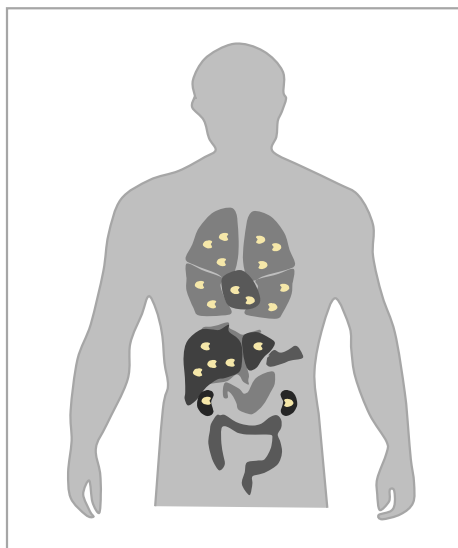
David A. Spiegel, MD, PhD

Yale Lifesciences Pitchfest / December 12, 2018

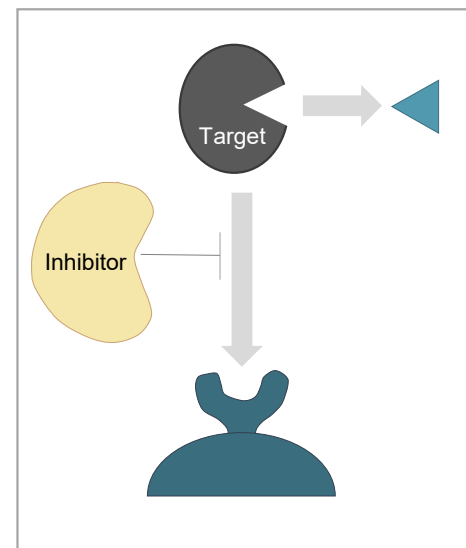
Challenges with Conventional Inhibitors



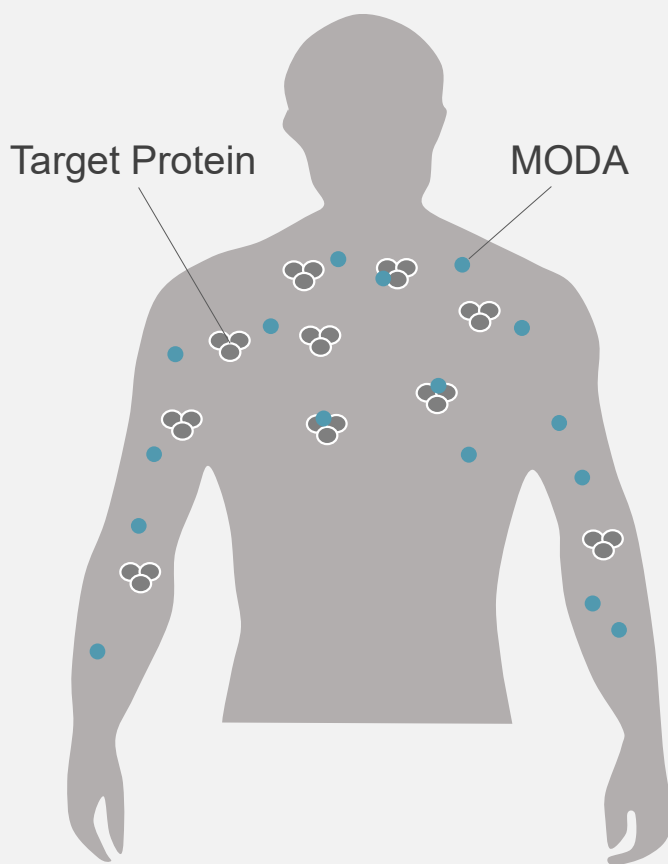
Occupancy of target is required for drug activity, which mandates sustained exposure to drug substance



Toxicity due to requirement of large systemic drug concentrations to ensure sufficient functional inhibition



Only a specific activity of target is controlled and may not result in loss of function of other activities

















Our Approach: The MODA Platform

- MODA Pharmaceuticals is built around a novel technology platform that enables development of **customizable small molecules** for **targeted elimination** of **extracellular proteins**
- MODA small molecules are designed to **bind to extracellular target proteins** and cause them to be **removed from the body**
- Existing targeted small molecule strategies (e.g. Kymera, Arvinas, C4) focus on eliminating **intracellular not extracellular** proteins

KEY FEATURES:

- Extracellular protein targets are eliminated as opposed to inhibited
- MODA therapeutics can be small molecule- or antibody-based
- Small molecule-based design opens up avenues for oral administration
- Potential to reduce drug exposure and off-target effects

Competitive Landscape for Immunoglobulin-Targeting Technologies

	Company	Technology Platform	Technology	Mode of Action
Therapeutics	Hansa Medical	Enzyme	Immunoglobulin G-degrading enzyme of <i>Streptococcus pyogenes</i> (IdeS)	Cleaves human IgG at the hinge region producing F(ab') ₂ and Fc fragments, cleaved IgG is unable to activate complement and promote other pathogenic processes
		Antibody	Efgartigimod- Human IgG1 Fc-fragment designed using ABDEG™ technology	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
		Antibody	SYNT001- Humanized monoclonal antibody engineered to have high affinity for FcRn	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
		Antibody	M281- Fully Human Fab aglycosylated IgG1 monoclonal antibody	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
		Antibody	Rozanolixizumab- a humanized high-affinity anti-human neonatal Fc receptor (FcRn) monoclonal antibody (IgG4P)	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
Plasmapheresis/IVIG	         			

**THE MODA
ADVANTAGE**



MODA Pharmaceuticals

David A. Spiegel, MD, PhD

Email: david.spiegel@yale.edu

Office: 203-432-8697

EXHIBIT 22

From: Wiesler, William [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=FA3C3C1BE2AC4BBB903185EEF1F8503B-WW84]
Sent: 1/14/2019 11:33:08 AM
To: Lewin, David [david.lewin@yale.edu]
CC: Puziss, John [john.puziss@yale.edu]; Milind Deshpande [mdeshpande@racap.com]; Kate Moreau [kmoreau@racap.com]
Subject: Re: Meetings with Peter Kolchinsky

Hi Millind,

Just seeing this. Sadly I'm out of town that day also.

I'm going to send you and Kate access to our Blavatnik portal. It will have videos and decks of everything at Pitchfest, plus another 32 projects that weren't at Pitchfest.

Best,

Bill

Sent from my iPhone

On Jan 14, 2019, at 11:06 AM, Lewin, David <david.lewin@yale.edu> wrote:

Hi Milind,

I am generally available to meet on February 12th and I am working with

- Alanna Schepartz – Exolva cytosolic delivery platform
- Nenad Sestan – Organ preservation/maintenance/reviving
- David Spiegel – MODA protein degradation platform
- Bill Jorgensen – Small molecule antagonists of MIF

Please let me know what you have in mind for that day so I can tell them what to expect from a meeting.

Best,

Dave

David A. Lewin, PhD

Sr. Associate Director Business Development

Yale University Office of Cooperative Research

P: 1-203-785-6038

F: 1-203-785-6165

E: david.lewin@yale.edu

Yale Partnering Opportunities

Save the date for the Yale Innovation Summit, May 8, 2019

From: Puziss, John

Sent: Friday, January 11, 2019 2:49 PM

To: Milind Deshpande <mdeshpande@racap.com>

Cc: Kate Moreau <kmoreau@racap.com>; Lewin, David <david.lewin@yale.edu>; Wiesler, William <bill.wiesler@yale.edu>

Subject: Re: Meetings with Peter Kolchinsky

I'd suggest coordinating with Bill Wiesler or Dave Lewin, since he works with all of those PI's except Aaron Ring.

Best,

John

--

John W. Puziss, Ph.D.
Director of Business Development
Office of Cooperative Research
Yale University
2 Church St. South, Suite 203
New Haven, CT 06519

Google Maps: <https://goo.gl/maps/nhC98ybpC9o>

(203) 785-6167
(203) 785-6165 (Fax)
john.puziss@yale.edu
www.yale.edu/ocr

On Jan 11, 2019, at 2:43 PM, Milind Deshpande <mdeshpande@racap.com> wrote:

John,

It's unfortunate that you and Jon have a conflict. Since Peter's presentation date at Yale Law School is set for Feb 12, we would still like to set up meeting with Yale PIs, and look for another date for a meeting with you and Jon. Is there some one else we can work with to coordinate these meetings (Bill or Chris?).

Thanks,
Milind

On Fri, Jan 11, 2019 at 9:24 AM Puziss, John <john.puziss@yale.edu> wrote:

Hi Milind,

It turns out that both Jon and I are away at a conference on the 12th. Should we look to reschedule for another date?

Best,
John

--

John W. Puziss, Ph.D.
Director of Business Development
Office of Cooperative Research
Yale University
2 Church St. South, Suite 203

New Haven, CT 06519

Google Maps: <https://goo.gl/maps/nhC98ybpC9o>

[\(203\) 785-6167](tel:(203)785-6167)
[\(203\) 785-6165 \(Fax\)](tel:(203)785-6165)
john.puziss@yale.edu
www.yale.edu/ocr

On Jan 3, 2019, at 9:31 AM, Milind Deshpande <mdeshpande@racap.com> wrote:

Hi John,

Happy new year! Hope that you had restful holidays, and wish you a peaceful and a very successful 2019.

I am reaching out to ask for help in coordinating meetings between Yale faculty and Peter Kolchinsky (Managing Director at RA) for February 12. Peter is giving a talk at Yale Law School at 4 PM, and it will be great if he can meet with some of the PIs earlier in the day. Our initial list for 1-on-1 meetings is: Alanna Schepartz, Nenad Sestan, Aaron Ring, David Spiegel, Bill Jorgensen (let us know if you have other suggestions). A meeting with you and Jon S will also be very beneficial to establish a relationship between RA and Yale OCR.

Are you available for a quick call tomorrow (any time except 2-3) to discuss Peter's visit?

best regards,

Milind

--

Milind Deshpande, Ph.D.

Venture Partner

W: [617-778-2572](tel:617-778-2572) | M: [203-314-5810](tel:203-314-5810) | E: mdeshpande@racap.com



RA Capital Management, LLC

20 Park Plaza, Suite 1200 | Boston, MA 02116

www.racap.com

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--

Milind Deshpande, Ph.D.

Venture Partner

W: [617-778-2572](tel:617-778-2572) | M: [203-314-5810](tel:203-314-5810) | E: mdeshpande@racap.com



RA Capital Management, LLC

20 Park Plaza, Suite 1200 | Boston, MA 02116

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EXHIBIT 23

Moda follow up

From: "Spiegel, David" <david.spiegel@yale.edu>
To: Vlad Coric <vlad.coric@biohavenpharma.com>
Cc: Donnie McGrath <donnaie.mcgrath@biohavenpharma.com>
Date: Mon, 25 Mar 2019 17:24:43 -0400
Attachments: Moda_Non-Confidential Deck_2019-3.pptx (1.53 MB)

Hi Vlad and Donnie, I hope all is well with you both. [REDACTED]

Please let me know if there is any additional information that I can provide, or if there are any questions, and I look forward to following up!

Best,
David

--

David A. Spiegel, Ph.D., M.D.
Yale University
Professor of Chemistry and Pharmacology
Website: <http://www.spiegelgroup.yale.edu/>

U.S. Mailing Address:
225 Prospect Street
P.O. Box 208107
New Haven, CT 06520-8107

Shipping (Fedex, UPS) Address:
350 Edwards Street
New Haven, CT 06511

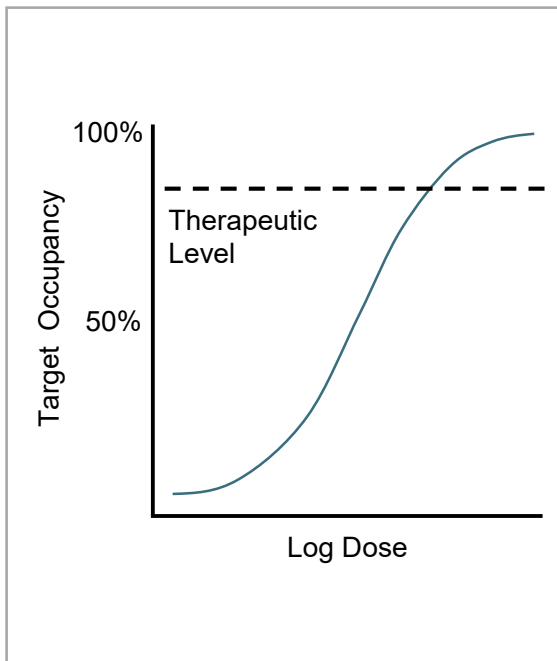
Office: 203-432-8697
Cell: 646-246-2159
Fax: 203-432-6144

The contents of this email are CONFIDENTIAL property of Yale University and/or David Spiegel.

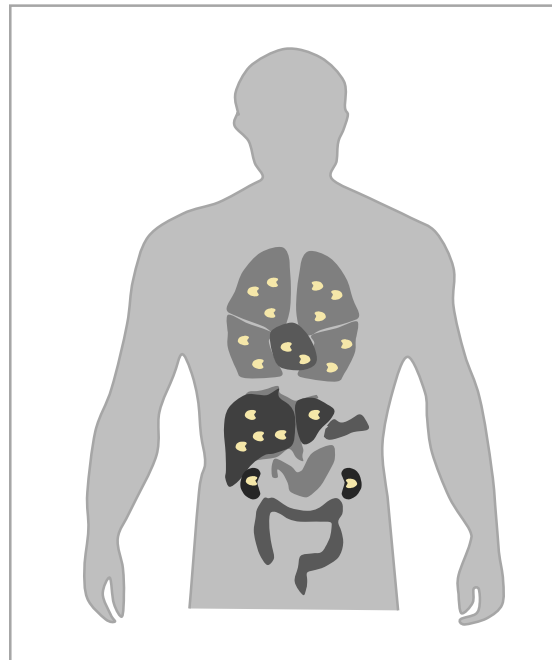
MODA Pharmaceuticals

Targeted Elimination of Pathogenic Extracellular Proteins

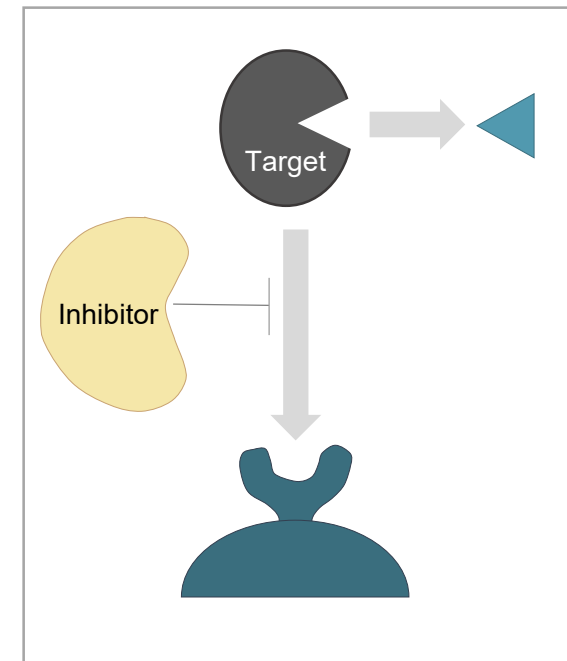
David A. Spiegel, MD, PhD



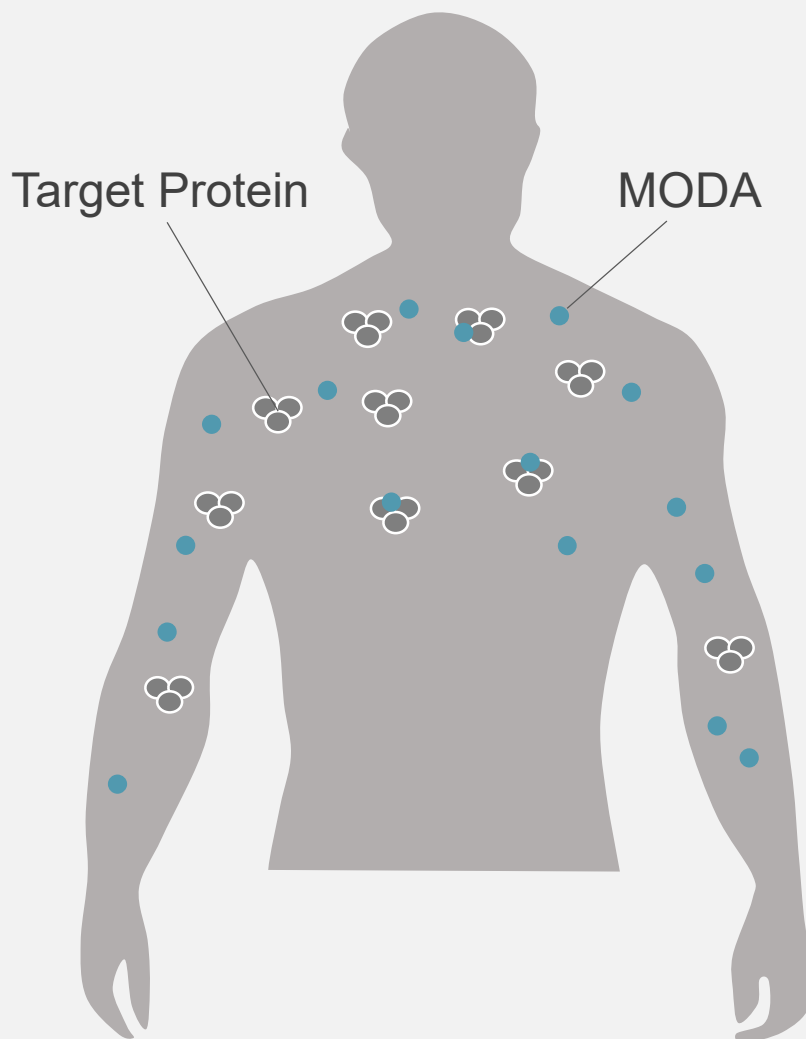
Occupancy of target is required for drug activity, which mandates sustained exposure to drug substance



Toxicity due to requirement of large systemic drug concentrations to ensure sufficient functional inhibition



Only a specific activity of target is controlled and may not result in loss of function of other activities













Our Approach: The MODA Platform

- MODA Pharmaceuticals is built around a novel technology platform that enables development of **customizable small molecules** for **targeted elimination** of **extracellular proteins**
- MODA small molecules are designed to **bind to extracellular target proteins** and cause them to be **removed from the body**
- Existing targeted small molecule strategies (e.g. Kymera, Arvinas, C4) focus on eliminating **intracellular not extracellular** proteins

KEY FEATURES:

- Extracellular protein targets are eliminated as opposed to inhibited
- MODA therapeutics can be small molecule- or antibody-based
- Small molecule-based design opens up avenues for oral administration
- Potential to reduce drug exposure and off-target effects

Competitive Landscape for Immunoglobulin-Targeting Technologies

	Company	Technology Platform	Technology	Mode of Action
Therapeutics	Hansa Medical	Enzyme	Immunoglobulin G-degrading enzyme of Streptococcus pyogenes (IdeS)	Cleaves human IgG at the hinge region producing F(ab') ₂ and Fc fragments, cleaved IgG is unable to activate complement and promote other pathogenic processes
	argenx	Antibody	Efgartigimod- Human IgG1 Fc-fragment designed using ABDEG™ technology	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
	ALEXION syntimmune	Antibody	SYNT001- Humanized monoclonal antibody engineered to have high affinity for FcRn	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
	MOMENTA	Antibody	M281- Fully Human Fab aglycosylated IgG1 monoclonal antibody	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
	ucb	Antibody	Rozanolixizumab- a humanized high-affinity anti-human neonatal Fc receptor (FcRn) monoclonal antibody (IgG4P)	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
Plasmapheresis/IVIG	<div>      </div> <div>      </div>			

**THE MODA
ADVANTAGE**



- Our technology focuses on **elimination** of extracellular protein targets instead of **inhibition**
- Platform can be applied to multiple disease-relevant targets and treat diverse patient populations
- We have achieved *in vivo* proof-of-concept for two targets and cellular proof-of-concept for one additional target.
- Two provisional patent applications have been filed and two more are in preparation

MODA Pharmaceuticals

David A. Spiegel, MD, PhD

Email: david.spiegel@yale.edu

Office: 203-432-8697

EXHIBIT 24

From: Ben Dake <bdake@racap.com>
Sent: 5/13/2019 12:40:32 PM
Subject: Re: MODA Chemistry assessment

What about the Craig Crews paper?

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Craig was on my thesis committee
intro'd me to Stuart Scrheiber for my post-doc
he has been a great positive force for me

David wants to close before the end of the month
David is available feel free call his cell any time

EXHIBIT 25

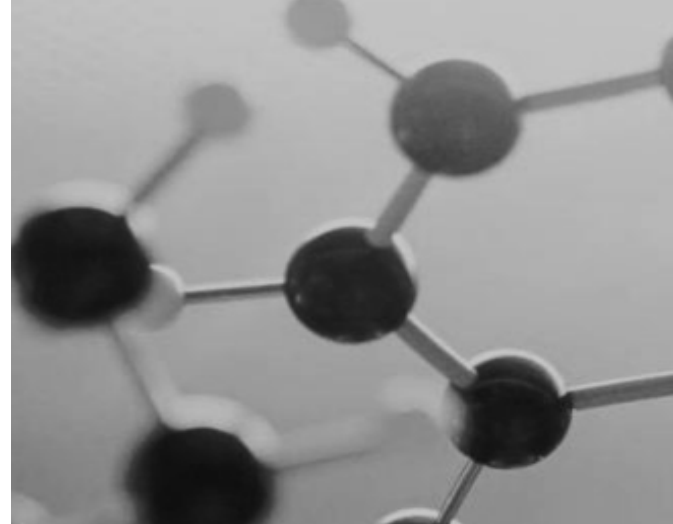
AbbVie–Spiegel Lab–MODA Collaboration

Targeted Elimination of Pathogenic Extracellular Proteins

David A. Spiegel, MD, PhD

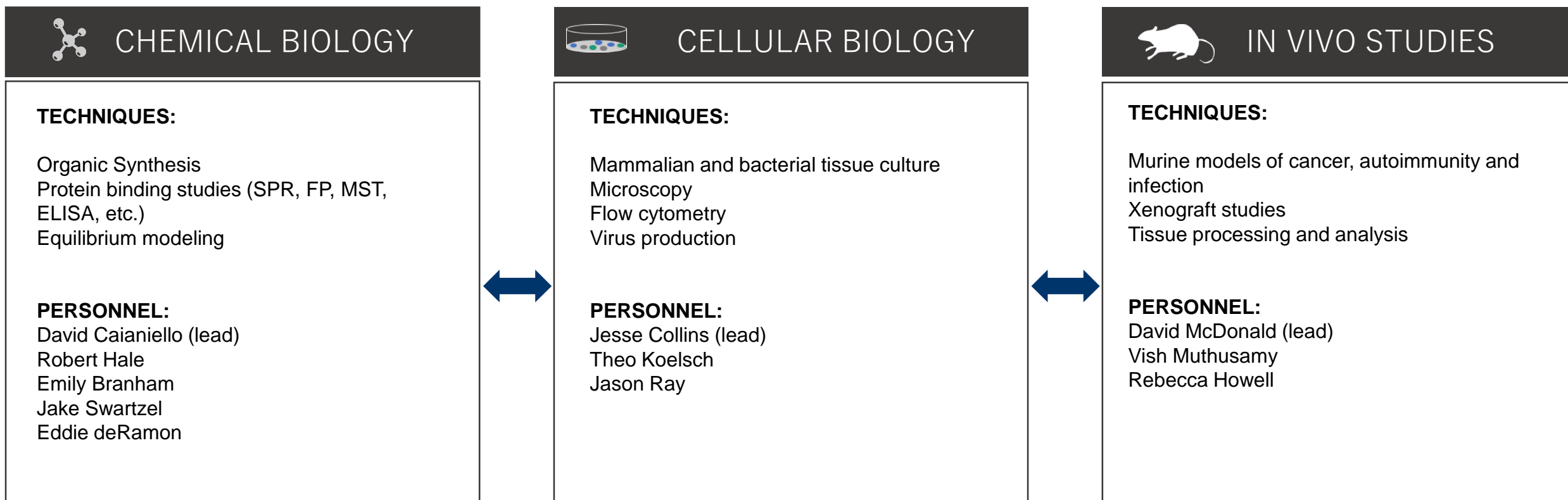


SPIEGEL RESEARCH GROUP



LAB OVERVIEW

The central focus of the Spiegel Research Group is the development of novel, small molecule-based strategies for manipulating and regulating human immunity and biological processes. The strategies we develop allow us to study the molecular mechanisms that underlie human diseases and design novel therapeutic approaches to address a number of pathologic conditions. Studies performed in the Spiegel Laboratory have significantly contributed to both fundamental and applied areas of research.



CHEMICAL BIOLOGY TEAM



DAVID CAIANIELLO
CHEMICAL BIOLOGY LEAD

Dave is a native of Rhode Island. He became interested in the biological applications of chemistry as an undergraduate at Brown University, where he used an under-appreciated method for measuring light absorption to determine how dyes stack in water. In the Spiegel Lab he is working on the development of new bifunctional molecules.



ROBERT HALE

Robert was born in New York City and grew up in Astoria, NY, and Little Silver, NJ. Robert did his undergraduate training in engineering and chemistry at the Stevens Institute of Technology. He performed mass spectrometric studies of oxalate and carbonate salts for his undergraduate research before earning a B. S. in chemistry in May 2015. In the Spiegel Lab, Robert is working to extend the methodology developed for glucosepane to access other natural products.



EMILY BRANHAM

Emily was born and raised in Georgia. She earned a chemistry BS, a biology minor, and a creative writing minor from UNC Chapel Hill. As an undergraduate, she discovered her love for chemistry research during her first summer research program, a chemistry REU at Georgia Tech. In the Spiegel lab, she is working on the synthesis and analysis of bifunctional molecules with possible therapeutic applications.

CHEMICAL BIOLOGY TEAM (continued)



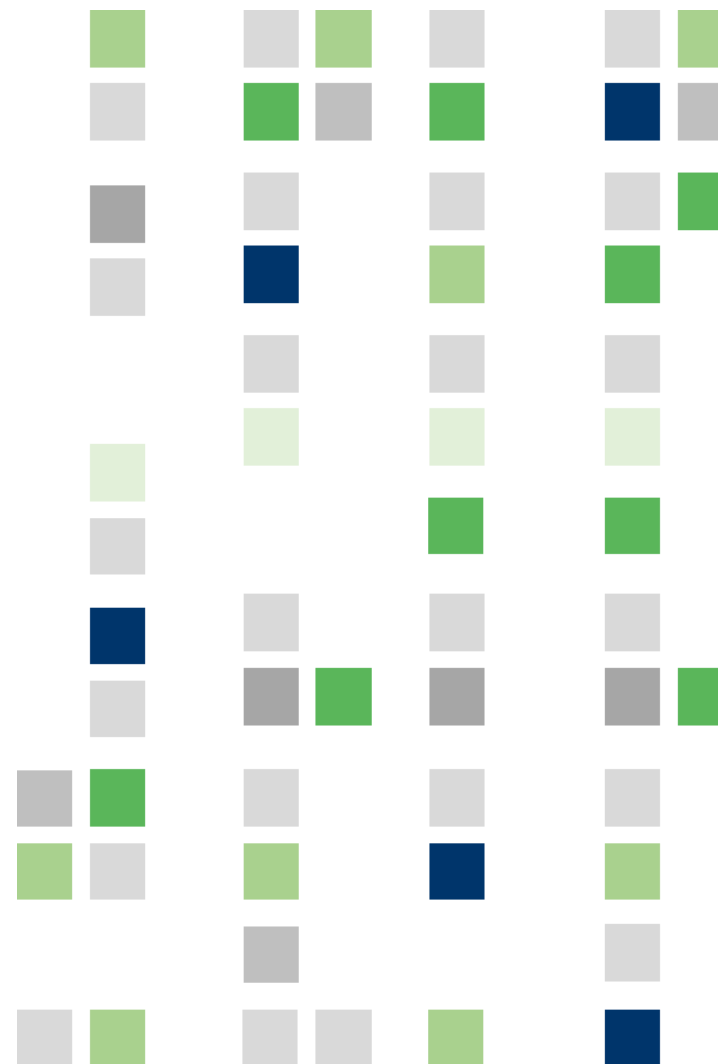
JAKE SWARTZEL

Jake grew up outside Boston, and moved to pursue a B.S. in Biochemistry at The University of Texas at Austin. While an undergraduate, his advanced coursework focused on organic chemistry and synthetic biology. He conducted research in the laboratory of Dr. Walter Fast toward the development of novel covalent enzyme inhibitors. In the Spiegel lab, he works on designing novel bifunctional molecules.



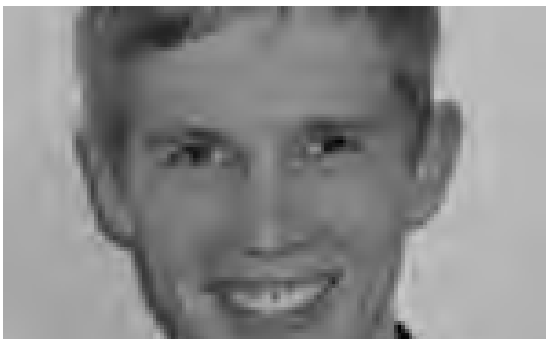
EDDIE deRAMON

Eddie grew up in New York where he attended SUNY New Paltz, majoring in Chemistry. There, his research was primarily focused in organic chemistry, while a summer research program at Johns Hopkins University opened him up to chemical biology. He began his PhD in Chemical Biology at Yale in 2018, where his combined interest in these research areas led him to join the Spiegel lab. Here, his work is primarily focused on the development of therapeutically relevant bifunctional molecules.



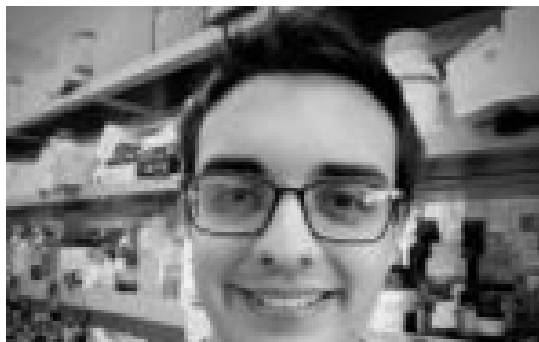


CELLULAR BIOLOGY TEAM



JESSE COLLINS
CELLULAR IMMUNOLOGY LEAD

Jesse grew up in Northern California, and pursued a B.A. in Molecular Biology at U.C. Berkeley. During his time there, Jesse worked in a lab studying dengue virus and took classes focused on immunology and bioengineering. Jess then went on to join the Spiegel lab to work at the interface of synthetic chemistry and molecular biology. He is now working on engineering immune-modulating proteins controlled by bifunctional small molecules.



THEO KOELSCH

Theo grew up in Colorado and attended CU Boulder, majoring in Chemistry, Biochemistry, and Music. At CU, he worked in the lab of Dr. Zhongping Tan, using insights into the effects of specific glycosylation to develop a bivalent HIV entry inhibitor from a small molecule and a glycosylated peptide. In the Spiegel Lab, he is investigating the function of advanced glycation end products, which may have therapeutic implications for multiple diseases.



JASON RAY

Jason grew up in North Carolina, and decided at age ten to become a scientist. He studied chemistry at Brigham Young University, where his coursework focused on organic chemistry and biochemistry. He did research with Dr. Jeffery Tessem on genetic pathways that could be targeted to reverse type 1 and type 2 diabetes. His research in the Spiegel lab focuses on novel uses of bifunctional molecules.



IN VIVO TEAM



DAVID MCDONALD, PHD
IN VIVO STUDIES LEAD

Born and raised in Sydney, Australia, David studied chemistry, immunology and biochemistry at the University of Sydney. He went on to study the deleterious activation of naïve CD8⁺ T lymphocytes in the liver at the Centenary Institute under the tutelage of Dr Patrick Bertolino. David returned to the University of Sydney for his PhD studies, under the supervision of Professor Richard Payne and Associate Professor Scott Byrne. In the Spiegel lab, David is working towards novel methods to rapidly identify small molecules that target specific proteins and cells..



VISH MUTHUSAMY, PHD

Vish earned his PhD from Madurai Kamaraj University. He went on to train at the University of Vermont and then took on the role of Associate Research Scientist at the Yale School of Medicine. Vish later joined the Spiegel lab as a Research Scientist. During his time with the group, Vish led pre-clinical studies to validate antibody mimicking small molecule immune therapeutics directed against cancer and pathogenic organisms. He currently serves as the Executive Director at the Center for Precision Cancer Modeling at Yale University.



REBECCA HOWELL

Rebecca grew up in Connecticut and attended Bucknell University where she majored in Cell Biology/ Biochemistry. After graduation, she completed a one-year appointment in the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center in Dr. Joern Schmitz's laboratory. She then joined the Immunology team at Moderna Therapeutics and worked under the guidance of Dr. Gilles Besin for three years. In the Spiegel lab her work focuses on the interface between chemistry and immunology.

Technology Update

Follow up on AbbVie Technical Questions

Design and Screening of GPCR ligands



- High throughput *in silico* docking experiments performed in collaboration with Dr. Matthew Welsch
- 96 commercially-available, non-glycomimetic, druglike compounds identified for **screening**:
- Soluble ASGPR available for SPR, microscale thermophoresis
- Immobilized ASGPR adopts trimeric conformation and can be screened using DELs or flexizyme technology (PeptiDream collaboration)
- Studies would constitute the first non-glycomimetic ligand identification exercise for ASGPR

JACS, 2017 Feb 23;139(9):3528-36

AbbVie Scope of Research Support

AbbVie-Yale int

Paths to Value

SubQ Product
Quick to the clinic

Oral Product
Maximizing impact

Platform Advancement
Capturing the space

Collaboration will be central to success....

abbvie



Yale

Target selection

Ligand discovery

Basic and mechanistic science

Medicinal chemistry

Construct validation

In vitro and *in vivo* Pharmacology

Platform Advancement

- **Mechanism** – fundamental studies of how extracellular protein degradation works and can be optimized
- **Alternative degradation pathways** – other non-ASGPR approaches (advancing the platform)
- **Alternative targeting modalities** – antibodies, antigen mimics, etc.
- **Immune response to degradation** – what impact does degradation have on immune response and how we can exploit
- **Trifunctional molecules**
 - Combination intra-, extra-cellular degraders
 - Degrading proteins in the brain

M

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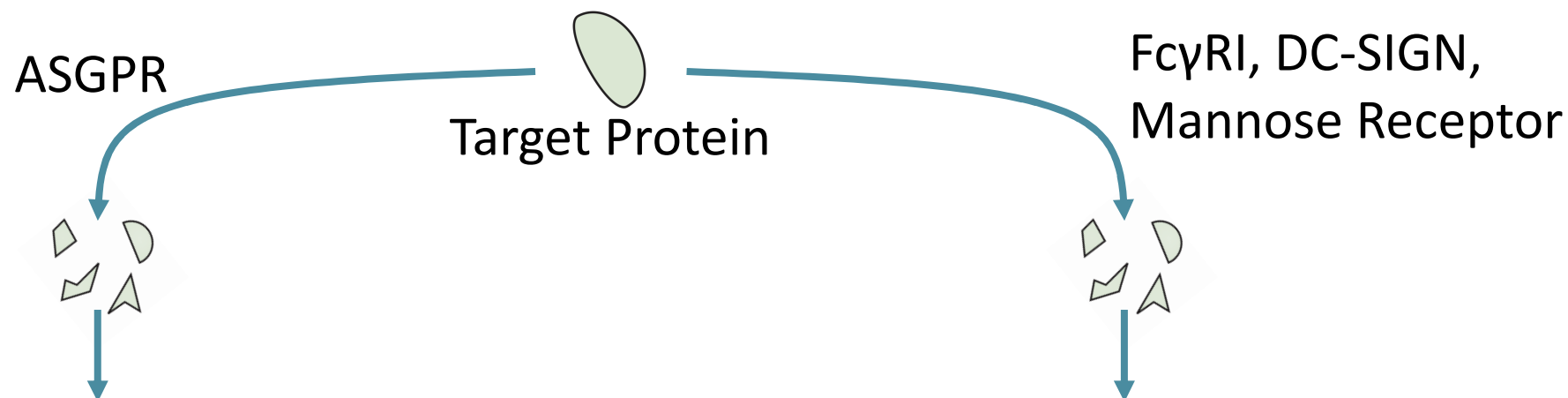
- Are there auxiliary pathways to ASGPR by which proteins are degraded physiologically?
 - ASGPR knockouts remain able to degrade circulating proteins, how is this happening?
- How does first-pass ASGPR binding impact efficacy following oral administration?
- How can recycling/catalysis of ligands be manipulated? Are kinetic or thermodynamic parameters more important?
- How does valency versus affinity impact targeted protein degradation? What is the influence of ASGPR multimerization on internalization and recycling?

Alternative Endocytic Receptors of Bifunctional Molecules

LRP-1	LDL-R	Mannose Receptor	Mannose-6P Receptor
<p>Main Functions: Receptor mediated endocytosis, cell motility, cell signaling</p> <p>Ligands:</p> <ul style="list-style-type: none"> - Several 10-100 nM binding peptides reported <p>Unique Applications:</p> <ul style="list-style-type: none"> - Crosses the BBB, so targeting to LRP-1 could be useful as a blood-brain shuttle <p><i>Biochemistry and biophysics reports, 12, 135-139</i></p>	<p>Main Functions: Mediates endocytosis of cholesterol-rich LDL</p> <p>Ligands:</p> <ul style="list-style-type: none"> - 10-20 nM peptides reported, 2-5 hour half-lives in mouse blood. <p>Unique Applications:</p> <ul style="list-style-type: none"> - LDLR targeting has been shown to allow delivery of small molecules and proteins <p><i>PLoS one, 13(2), e0191052.</i></p>	<p>Main Function: Receptor mediated endocytosis</p> <p>Ligands:</p> <ul style="list-style-type: none"> - Sulfated carbohydrates, collagen, mannose and mannose polymers <p>Unique Applications:</p> <ul style="list-style-type: none"> - Mannose-receptor targeting vaccines have been developed due the high level of MR expression on APCs <p><i>Expert opinion on biological therapy 4.12 (2004): 1953-1962</i></p>	<p>Main Function: Targeting lysosomal enzymes to the lysosome by cycling between <i>trans</i>-golgi and lysosome. Also modulates activity of various extracellular M6P-glycoproteins</p> <p>Ligands: Sulfated carbohydrates, M6P analogs</p> <p>Unique Applications:</p> <ul style="list-style-type: none"> - Bifunctional molecules for targeting lysosomal storage disorders - Glucocerebrosidase

Immunological Consequences of Targeted Protein Degradation

Goal: Understand and control impact of targeted extracellular protein degradation on tolerance and immunity



Tolerance

- Can targeted degradation through ASGPR prevent or reverse immune responses to protein targets?
- What is the mechanism through which tolerization takes place in hepatocytes?

Applications:

- Prevention/reversal of immunological reactions towards therapeutic proteins, antibodies
- Tolerization of the target antigens in allergy, autoimmunity

Immunity

- Can bifunctional molecules targeting immunogenic degradative receptors induce immune responses to target proteins?
- Can we break tolerance to self proteins?

Applications:

- Concomitant degradation and immune stimulation towards cancer antigens, pathogen toxins, etc.

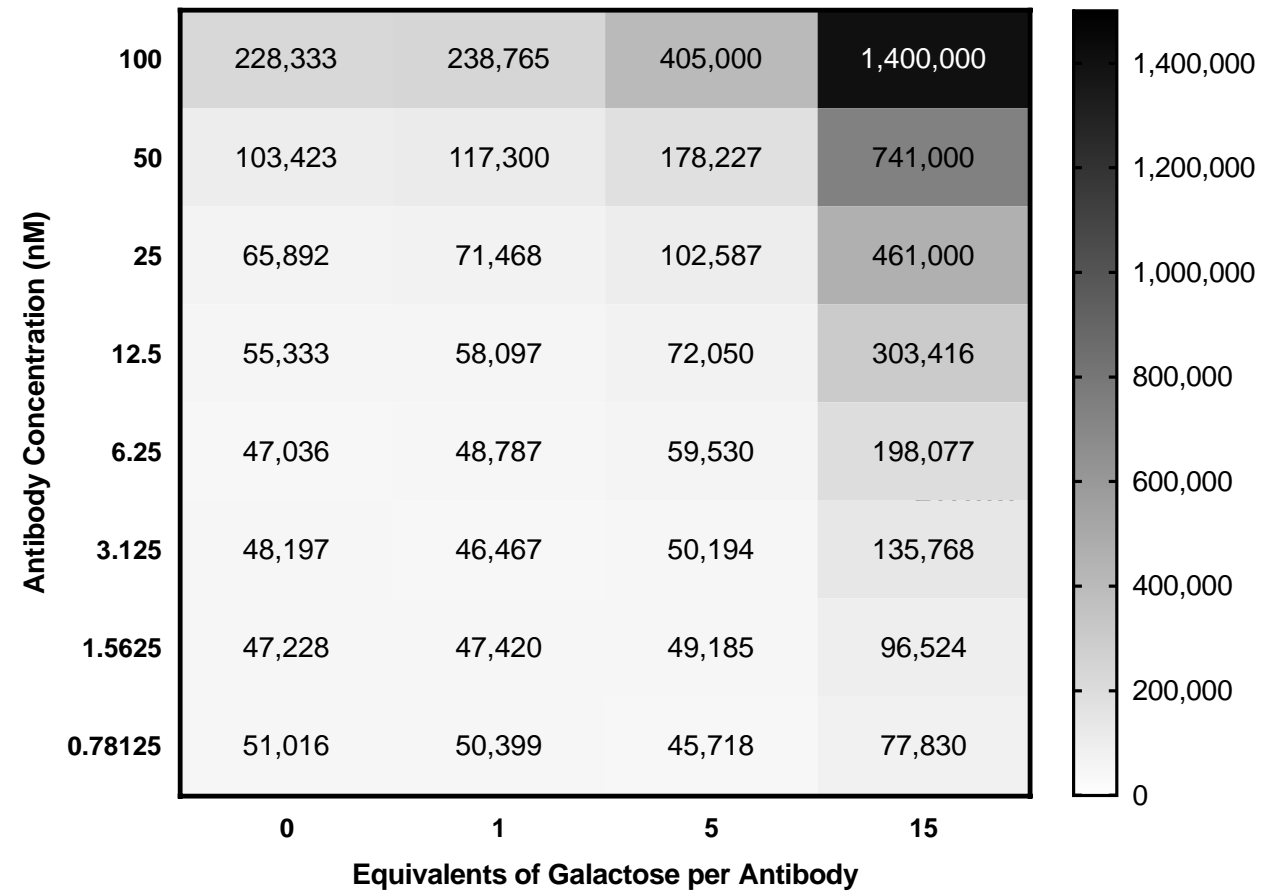
Antib

DAs

Can antibodies and/or other modalities be used to target proteins to hepatocytes for ASGPR mediated degradation?

- Our technology functions extracellularly so small molecule is not necessary
- Targets that degrade more slowly than antibodies should be viable
- **PCSK9** as target
 - Conditions: high cholesterol, heart disease, heart attack, stroke
- Found that antibody uptake increases with increasing galactose conjugation number
- **Next steps:**
 - PCSK9 uptake trends with anti-PCSK9 uptake in this system
 - Can other modalities (aptamers, nanoparticles) also prove useful?

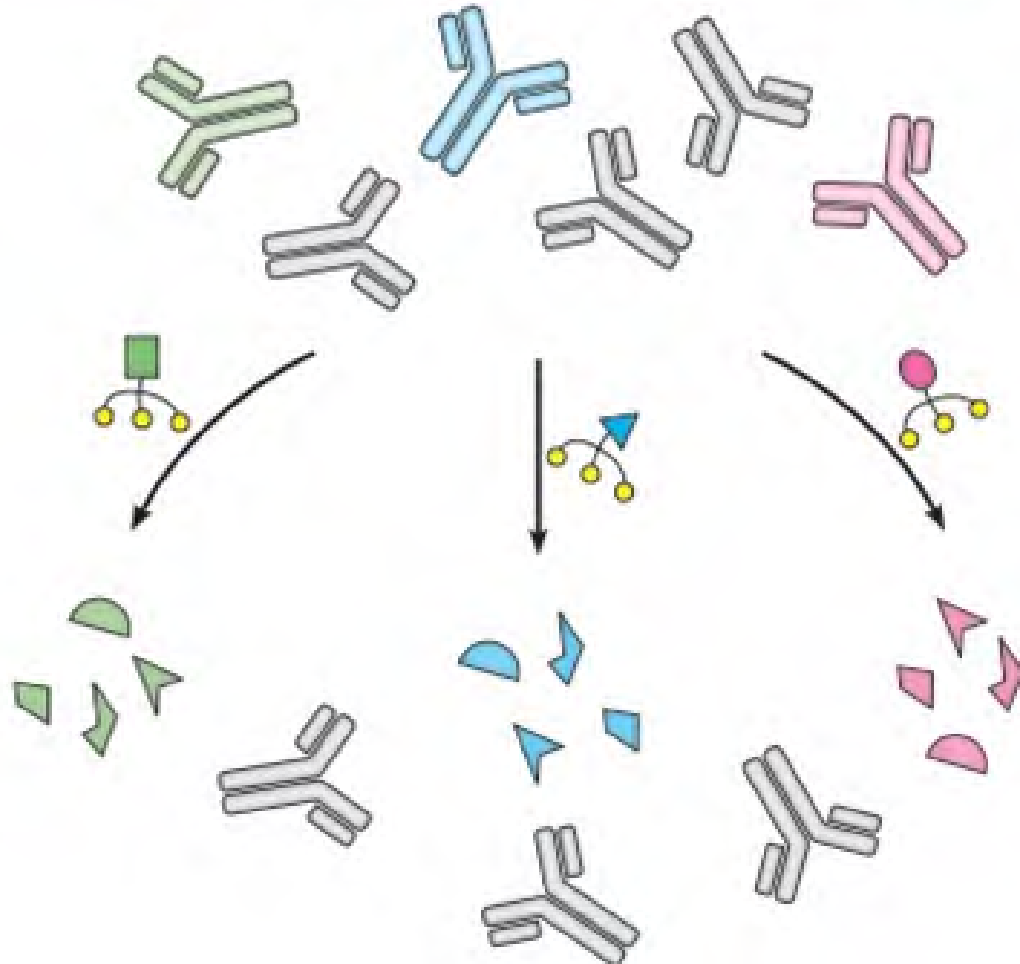
anti-PCSK9 antibody modified with indicated number of galactose equivalents...



Rheumatoid Arthritis
anti-citrullinated proteins

Cardiomyopathy
anti-beta-1-adrenergic receptor

Lupus
anti-dsDNA



- RA, CM and SLE all represent unmet medical challenges
- Low molecular weight mimics for autoantigens exist for all three autoantibodies, even despite their polyclonality
- The therapy would be highly specific and will prevent immunosuppression caused by alternative treatments (plasmapheresis, FcRn inhibitors)
- Degradation will enhance efficacy versus inhibition alone

VanPatten S et al. *Journal of Medicinal Chemistry*, **2016**; 59(19):8859-67.
Patel PA, Hernandez AF. *European journal of heart failure*. **2013**; 15(7):724-9.
Holoshitz J. *Current opinion in rheumatology*. **2010**; 22(3):293.

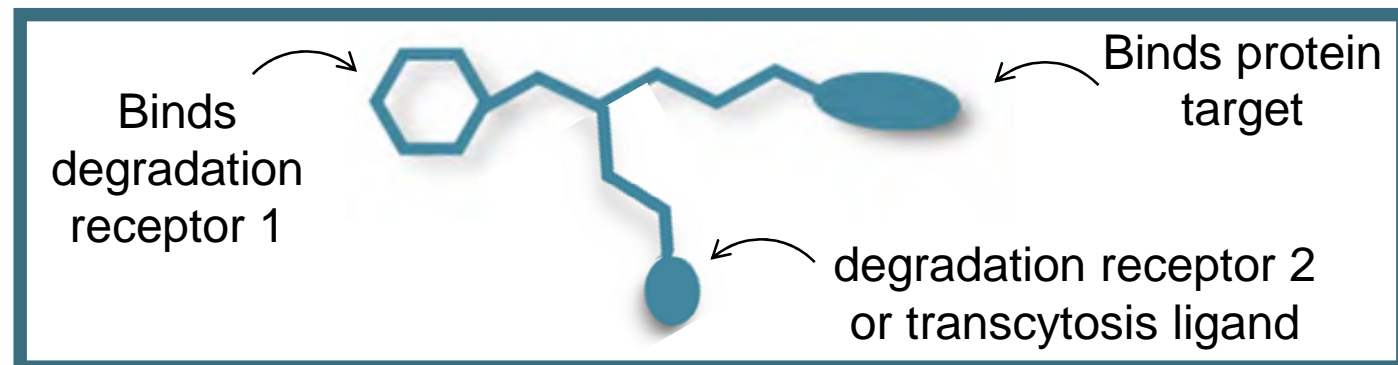
Targeting Using Small Molecules

Intra-/Extracellular Degraders:

- **Hypothesis:** Targeting both E3 ligase and ASGPR systems will enable removal or proteins with intra- and extracellular localization
- **Applications:** Alzheimer's Disease (tau), fibrosis (LOXL2), Parkinson's (synuclein)

Degrading proteins in CNS:

- **Hypothesis:** Targeting transcytotic receptors will facilitate entry and exit of proteins across the blood brain barrier, degradation will occur in liver
- **Applications:** Alzheimer's Disease (tau, α -beta)



Transcytosis ligands	Example(s)	Ligands
BBB-Receptors	LDL receptor-related protein 1 Transferrin receptor CD98hc	Several peptide or antibody options
BBB-Viral peptides	Peptidyl-Targeting Vectors, "Peptide Shuttle"	DEN2C PepH3 RVG29
BBB-Transporters	Glut1 glucose transporter GSH glutathione transporter	Modified Cholesterol GSH

Nabi, et al. *Brain Research Bulletin*. **2018**. 142, 384.
 Ruan, H, et al. *Journal of Controlled Release*. **2018**. 279, 306.
 Sakamoto, K, et al. *Biochemistry and Biophysics Reports*. **2017**, 12, 135.
 Zuchero, et al. *Neuron*. **2016**. 89, 70

BUDGET

	SALARY	# OF MONTHS	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	TOTAL
SALARIES								
Spiegel, David, PI	\$204,970	1 (Summer)	22,774	23,458	24,161	24,886	25,633	120,912
Postdoctoral Associate, YR1+, TBN	\$50,760	12 (Calendar)	50,760	52,283	53,851	55,467	57,131	269,492
Postdoctoral Associate, YR1, TBN	\$50,004	12 (Calendar)	50,004	51,504	53,049	54,641	56,280	265,478
Graduate Student (6), TBN	\$35,250	12 (Calendar)	32,250	36,308	37,397	38,519	39,674	187,148
SALARIES SUB-TOTAL			335,038	345,093	355,443	366,108	377,088	1,778,770
FRINGE BENEFITS (27.50%) G&C EXEMPT								
Spiegel, David, PI			6,263	6,451	6,644	6,844	7,049	33,251
Postdoctoral Associate, YR1+, TBN			13,959	14,378	14,809	15,253	15,711	74,110
Postdoctoral Associate, YR1, TBN			13,751	14,164	14,588	15,026	15,477	73,006
TOTAL PERSONNEL			369,011	380,086	391,484	403,231	415,325	1,959,137

BUDGET

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	TOTAL
TRAVEL						
Domestic	7,000	7,000	7,000	7,000	7,000	35,000
Foreign	10,000	10,000	10,000	10,000	10,000	50,000
TOTAL TRAVEL	17,000	17,000	17,000	17,000	17,000	85,000
MATERIALS AND SUPPLIES						
Lab Supplies	70,000	70,000	70,000	70,000	70,000	350,000
Nitrogen gas, liquid N2, dry ice	1,500	1,500	1,500	1,500	1,500	7,500
TOTAL SUPPLIES	71,500	71,500	71,500	71,500	71,500	357,500

BUDGET











	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	TOTAL
OTHER DIRECT COSTS						
In vivo Work	245,589	228,668	211,161	193,031	174,266	1,052,715
Equipment/Services	150,000	150,000	150,000	150,000	150,000	750,000
Waste Disposal	1,500	1,500	1,500	1,500	1,500	7,500
Instrument Center Costs	15,000	15,000	15,000	15,000	15,000	75,000
Shipping	500	500	500	500	500	2,500
Tuition	129,900	135,746	141,855	148,238	154,909	710,648
TOTAL OTHER DIRECT COSTS	542,489	531,414	520,016	508,269	496,175	2,598,363
TOTAL DIRECT COSTS	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	5,000,000
INDIRECT COSTS @ 69.90%	699,000	699,000	699,000	699,000	699,000	3,495,000
TOTAL COSTS	1,699,000	1,699,000	1,699,000	1,699,000	1,699,000	8,495,000

Thanks for visiting!!

AbbVie—Spiegel Lab—MODA Collaboration

David A. Spiegel, MD, PhD

Competitive Landscape for Immunoglobulin-Targeting Technologies

	Company	Technology Platform	Technology	Mode of Action
Therapeutics	Hansa Medical	Enzyme	Immunoglobulin G-degrading enzyme of Streptococcus pyogenes (IdeS)	Cleaves human IgG at the hinge region producing F(ab') ₂ and Fc fragments, cleaved IgG is unable to activate complement and promote other pathogenic processes
	argenx	Antibody	Efgartigimod- Human IgG1 Fc-fragment designed using ABDEG™ technology	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
	ALEXION syntimmune	Antibody	SYNT001- Humanized monoclonal antibody engineered to have high affinity for FcRn	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
	MOMENTA	Antibody	M281- Fully Human Fab aglycosylated IgG1 monoclonal antibody	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
	ucb	Antibody	Rozanolixizumab- a humanized high-affinity anti-human neonatal Fc receptor (FcRn) monoclonal antibody (IgG4P)	Targets and binds to FcRn, blocking the recycling of IgG and leading to the elimination of IgGs
Plasmapheresis/IVIG	<div>      </div> <div>      </div>			

**THE MODA
ADVANTAGE**

Asialoglycoprotein Receptor (ASGPR) Molecular Recognition

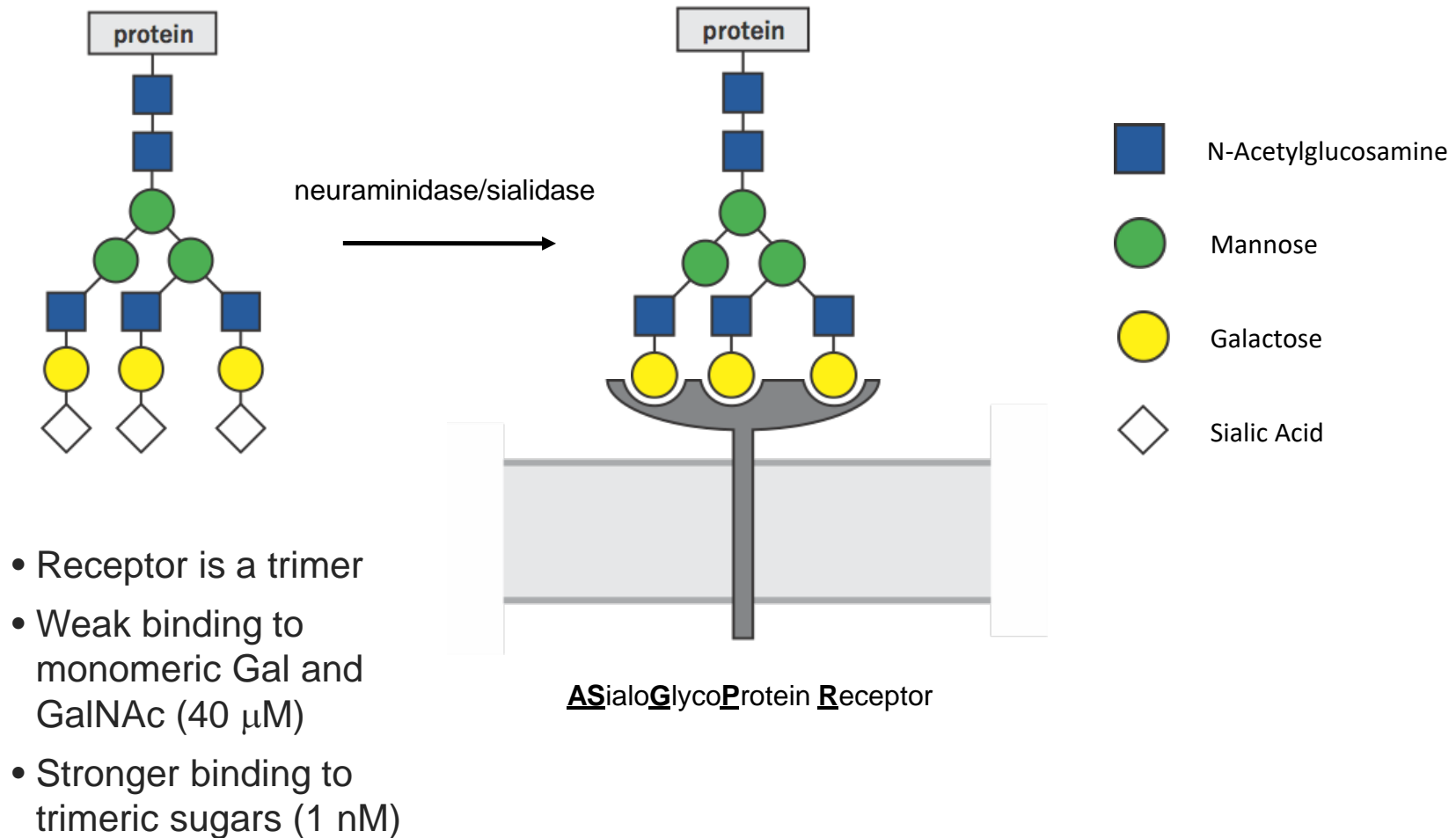


EXHIBIT 26

Anaba, Ariel

From: Evie Spanos <ESpanos@susmangodfrey.com>
Sent: Thursday, February 1, 2024 12:41 PM
To: WSGR - BiohaventvAvilar; KLG-Biohaven@klgates.com
Cc: Yale-SG-Farnan@simplelists.susmangodfrey.com
Subject: Yale/Biohaven v. RA Capital/Avilar: Yale's Production of Documents Pursuant to the Court's Order (D.I. 96)

EXT - espanos@susmangodfrey.com

Counsel,

The Court ordered Yale to “produce documents from Dr. Spiegel and members of his laboratory communicating with Dr. Crews and/or his laboratory about the alleged trade secrets and/or the ENDTAC technology.” After a reasonable and proportional search to date, Yale identified one communication from a member of Dr. Spiegel’s lab communicating with an individual working in the Crews Lab that related to the alleged trade secrets and/or the ENDTAC technology. Yale produces it as YALE00009845 – YALE00009902 at this previously shared link:

<https://susmangodfrey.sharefile.com/f/fo8449b5-37d3-4c75-b94d-00f240a81836>.

Sincerely,
Evie Spanos



Evie Spanos | Of Counsel
espanos@susmangodfrey.com
212.338.8830 (Office) | 617.549.0148 (Cell)
1301 Avenue of the Americas | 32nd Floor
New York, New York 10019
Houston | New York | Los Angeles | Seattle

EXHIBIT 27

From: David Caianiello [david.caianiello@yale.edu]
on behalf of David Caianiello <david.caianiello@yale.edu> [david.caianiello@yale.edu]
Sent: 8/3/2020 1:19:34 PM
To: Mengwen Zhang [mengwen.zhang@yale.edu]; Jason Ray [jason.ray@yale.edu]; Jake Swartzel [jake.swartzel@yale.edu]; Emily Branham [emily.janeira@yale.edu]; Egor CHIRKIN [egor.chirkin@pasteur.fr]; Angela Gong [angela.gong@yale.edu]; SABBASANI, VENKATAREDDY [venkatareddy.sabbasani@yale.edu]; Muthusamy, Viswanathan [vish.muthusamy@yale.edu]
Subject: Finalized ASGPR manuscript – ok to submit?
Attachments: 20200728 Supp .pdf; 20200731 main.pdf

Hi all – finalized version of the ASGPR manuscript attached. We plan on submitting this ASAP. Please let me know if you see any glaring errors or issues. Otherwise, please just let me know that – as an author – you've reviewed the manuscript.

Thanks!

Dave

EXHIBIT 28

Bifunctional Small Molecules That Mediate the Degradation of Extracellular Proteins

David Caianiello, Mengwen Zhang, Jason Ray, Jake Swartzel, Emily Branham, Egor Chirkin, Venkata Sabbasani, Angela Gong, David McDonald, Viswanathan Muthusamy, David Spiegel

Submitted date: 29/07/2020 • Posted date: 29/07/2020

Licence: CC BY-NC-ND 4.0

Citation information: Caianiello, David; Zhang, Mengwen; Ray, Jason; Swartzel, Jake; Branham, Emily; Chirkin, Egor; et al. (2020): Bifunctional Small Molecules That Mediate the Degradation of Extracellular Proteins. ChemRxiv. Preprint. <https://doi.org/10.26434/chemrxiv.12732689.v1>

Targeted protein degradation (TPD) has emerged as a promising and exciting therapeutic strategy. The majority of existing TPD technologies rely on the ubiquitin-proteasome system, and are therefore limited to targeting intracellular proteins. To address this limitation, we developed a class of modularly designed, bifunctional synthetic molecules called MoDE-As (Molecular Degraders of Extracellular proteins through the Asialoglycoprotein receptor (ASGPR)), which are capable of mediating the degradation of extracellular proteins. MoDE-A molecules mediate the formation of a ternary complex between a target protein and the ASGPR, which is expressed primarily on hepatocytes. The target protein is then endocytosed and degraded by lysosomal proteases. We demonstrated the modularity of the MoDE-A technology by synthesizing bifunctional molecules that induce the degradation of both antibody and pro-inflammatory cytokine proteins. To our knowledge, these data represent the first experimental evidence that non-proteinogenic, synthetic molecules can be employed for the TPD of extracellular proteins both in vitro and in vivo. We believe that TPD mediated by the MoDE-A technology will have widespread applications for disease treatment.

File list (2)

20200729 main.pdf (1.28 MiB)

[view on ChemRxiv](#) • [download file](#)

20200728 Supp .pdf (1.45 MiB)

[view on ChemRxiv](#) • [download file](#)

Title: Bifunctional small molecules that mediate the degradation of extracellular proteins

Authors: David F. Caianiello¹, Mengwen Zhang^{1,2}, Jason D. Ray¹, Jake C. Swartzel^{1,3}, Emily M. J. Branham¹, Egor Chirkin¹, Venkata R. Sabbasani¹, Angela Z. Gong¹, David M. McDonald¹, Viswanathan Muthusamy⁴, David A. Spiegel^{1,*}

Affiliations:

¹Department of Chemistry, Yale University. 225 Prospect Street, New Haven, CT 06511 (USA).

²Department of Molecular Biophysics and Biochemistry, Yale University. 266 Whitney Avenue, New Haven, CT 06511 (USA).

³Department of Molecular, Cellular, and Developmental Biology, Yale University. 260 Whitney Ave, New Haven, CT 06511 (USA).

⁴Yale Center for Precision Cancer Modeling, Yale University School of Medicine, New Haven, CT (USA).

*Correspondence to: david.spiegel@yale.edu

Abstract: Targeted protein degradation (TPD) has emerged as a promising and exciting therapeutic strategy. The majority of existing TPD technologies rely on the ubiquitin-proteasome system, and are therefore limited to targeting intracellular proteins. To address this limitation, we developed a class of modularly designed, bifunctional synthetic molecules called **MoDE-As** (**M**olecular **D**egraders of **E**xtracellular proteins through the **A**sialoglycoprotein receptor (ASGPR)), which are capable of mediating the degradation of extracellular proteins. MoDE-A molecules mediate the formation of a ternary complex between a target protein and the ASGPR, which is expressed primarily on hepatocytes. The target protein is then endocytosed and degraded by lysosomal proteases. We demonstrated the modularity of the MoDE-A technology by synthesizing bifunctional molecules that induce the degradation of both antibody and pro-inflammatory cytokine proteins. To our knowledge, these data represent the first experimental evidence that non-proteinogenic, synthetic molecules can be employed for the TPD of extracellular proteins both *in vitro* and *in vivo*. We believe that TPD mediated by the MoDE-A technology will have widespread applications for disease treatment.

One Sentence Summary: Bifunctional molecules that engage both a target protein and an endocytic receptor are able to induce the lysosomal degradation of extracellular proteins.

Main Text:

Extracellular protein levels are elevated in many different conditions, and technologies that mediate their removal from circulation have the potential to ameliorate a wide range of disease states (1, 2). One mechanism to decrease the serum concentration of an extracellular protein is to induce its endocytosis and subsequent degradation by lysosomal proteases. In order to accomplish

this goal, we developed a class of bifunctional molecules collectively termed **Molecular Degraders of Extracellular proteins** through the **Asialoglycoprotein receptor (MoDE-As)**. MoDE-A molecules mediate the formation of a ternary complex between a target protein and the endocytic asialoglycoprotein receptor (ASGPR). The target protein is then endocytosed, trafficked to lysosomes, and degraded by lysosomal proteases (Figure 1A). To validate our technology, we focused on inducing the degradation of a model antibody that binds dinitrophenol (DNP). We also expanded our technology to induce the uptake of the cytokine macrophage migratory inhibitory factor (MIF), which is implicated in numerous inflammatory diseases (3). The bifunctional molecules developed through this work represent the first reported extracellular protein degrading technology validated *in vivo*.

We chose to degrade proteins via ASGPR-dependent mechanisms for several reasons. ASGPR is primarily expressed on hepatocytes, which are capable of catabolizing large quantities of protein with minimal toxicity compared to other cell types (4-8). Indeed, ASGPR controls the half-lives of several endogenous circulating proteins, including hormones (9), alkaline phosphatases (10), and proteins terminating in Sia α 2,6Gal glycans (11). ASGPR also plays a role in controlling the concentration of platelets in serum (12). Because of its well-defined binding requirements (13) and its abundant expression on hepatocytes, ASGPR has been used extensively to deliver therapeutic agents to the liver (14-18). Ligands for ASGPR are also readily available. Molecules that display multiple galactose-type sugars – such as the desialylated serum glycoproteins that aided in the discovery of ASGPR (19) – bind strongly to the receptor (20). For example, the ASGPR-binding trivalent GalNAc motif utilized in MoDE-A molecules, which is similar to those used in previous studies (21), is estimated to bind to multimeric ASGPR with K_d values in the low nanomolar range (22).

ASGPR mediates protein endocytosis through a well-studied mechanism. Each functional receptor is composed of two or more ASGPR protein chains, each with an extracellular C-type lectin domain with modest affinity to N-acetylgalactosamine (GalNAc) and related carbohydrates (23). Following endocytosis, ASGPR's binding to its sugar ligands is disrupted, and the dissociated protein ligand is trafficked to lysosomes where it is ultimately degraded by lysosomal proteases (24, 25).

The bifunctional MoDE-A molecules developed in this work contain three domains: an ASGPR-binding motif, a PEG spacer, and a protein-binding ligand (Figure 1A). D-MoDE-A and M-MoDE-A share the same ASGPR binding motif, but feature different target-binding termini (Figure 1B). To bind to α -DNP antibodies, D-MoDE-A contains a dinitrophenyl group connected through a PEG linker to the ASGPR-binding motif. In contrast, the MIF-binding molecule M-MoDE-A was synthesized by incorporating a carboxylic acid-terminated MIF tautomerase inhibitor with a K_d of approximately 53 nM (26). Full synthetic methods and characterization are available in the supporting information.

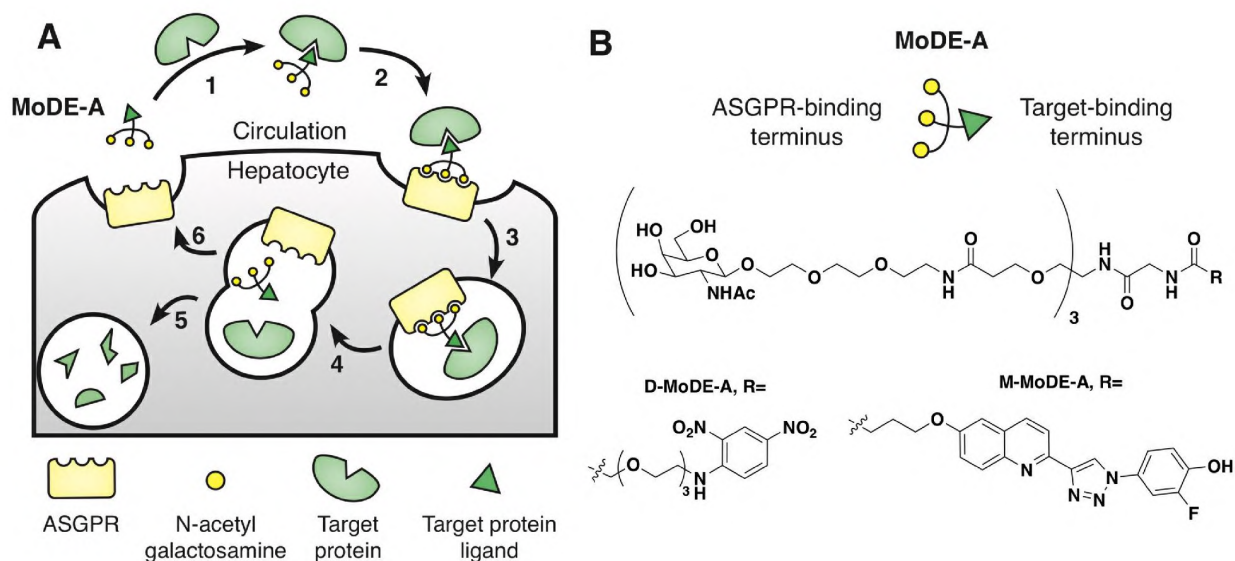


Figure 1: Bifunctional MoDE-A molecule design and chemical structures.

A) Schematic of uptake of target proteins via ASGPR mediated by MoDE-A bifunctional molecules.

B) Chemical structure of bifunctional molecules D-MoDE-A and M-MoDE-A.

- through nucleosides elicit robust gene silencing in vivo in hepatocytes. *ACS Chem. Biol.* **10**, 1181-1187 (2015).
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 17. A. M. Pujol, M. Cuillel, O. Renaudet, C. Lebrun, P. Charbonnier, D. Cassio, C. Gateau, P. Dumy, E. Mintz, P. Delangle, Hepatocyte targeting and intracellular copper chelation by a thiol-containing glycocyclopeptide. *J. Am. Chem. Soc.* **133**, 286-296 (2010).
 18. A. Akinc, W. Querbes, S. De, J. Qin, M. Frank-Kamenetsky, K. N. Jayaprakash, M. Jayaraman, K. G. Rajeev, W. L. Cantley, J. R. Dorkin, J. S. Butler, L. Qin, T. Racie, A. Sprague, E. Fava, A. Zeigerer, M. J. Hope, M. Zerial, D. W. Y. Sah, K. Fitzgerald, M. A. Tracy, M. Manoharan, V. Kotliansky, A. de Fuogerolles, M. A. Maier, Targeted delivery of RNAi therapeutics with endogenous and exogenous ligand-based mechanisms. *Mol. Ther.* **18**, 1357-1364 (2010).
 19. V. Bocci, The role of sialic acid in determining the life-span of circulating cells and glycoproteins. *Experientia* **32**, 135-140 (1976).
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EXHIBIT 29



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**Jake Swartzel, PhD** (He/Him) · 3rd

Chemist and Project Lead at Nurix Therapeutics

 Nurix Therapeutics Yale UniversitySan Francisco, California, United States · [Contact info](#)

490 connections

Message

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During my PhD I worked on the development of several novel and exciting bifunctional molecule technologies: PROTACs for new classes of protein targets, PhosTACs, protein half-life extension strategies, and ASGPR-targeted degraders (MoDE-As/LYTACs) for circulating proteins. If it forms a ternary complex or acts as a molecular glue, I'm interested in it!

I continue to work in the bifunctional molecule/TPD space, developing next-gen therapies at Nurix!

Outside of the lab, I like to do yoga, make music, get tattoos, and hang out with my cat.

Check out my music: <https://linktr.ee/skorpion دنب>

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Experience



Scientist, Project Lead, Medicinal Chemistry

Nurix Therapeutics · Full-time

Dec 2021 – Present · 2 yrs 3 mos

San Francisco Bay Area



PhD (Chemistry) - Craig Crews Laboratory - Yale

Yale University · Full-time

May 2017 – Dec 2021 · 4 yrs 8 mos

Education



Yale University

Doctor of Philosophy - PhD, Chemistry/Chemical Biology

May 2017 – Nov 2021



The University of Texas at Austin

Bachelor of Science - BS, Biochemistry

2013 – 2017

Skills

Organic Synthesis



Endorsed by Mehrdad (Mike) Shadmehr who is highly skilled at this



Endorsed by 1 people in the last 6 months



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From Jake's company




Paula OConnor 
SVP Clinical Development at Nurix Therapeutics

Connect



Christine Ring
General Counsel at Nurix Therapeutics, Inc.

Connect



Ge (Gina) Wei
Translational Medicine, clinical and CDx development, discovery and clinical biomarkers, preclinical and discovery research, IND and NDA...

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Bev Benson PhD
Vice President and Head of Clinical Science

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Cristiana Guiducci
Senior Vice President of immunology and Oncology Research at Nurix Therapeutics

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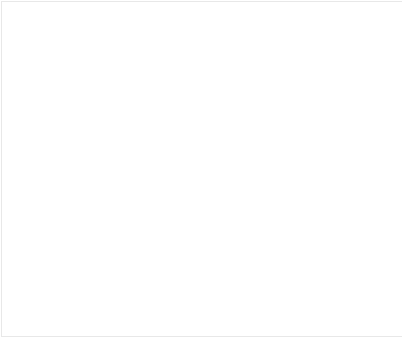


EXHIBIT 30

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

BIOHAVEN THERAPEUTICS, LTD. and
YALE UNIVERSITY,

Plaintiffs,

v.

C.A. No. 23-328-CFC

AVILAR THERAPEUTICS, INC., a Delaware
corporation, and RA CAPITAL
MANAGEMENT GP, LLC, a Delaware
corporation,

Defendants.

**PLAINTIFFS BIOHAVEN THERAPEUTICS, LTD. AND YALE UNIVERSITY'S
AMENDED ESI DISCLOSURES**

Pursuant to Section 2 of the October 12, 2023 Order Regarding Discovery of Electronically Stored Information [D.I. 68], Plaintiffs Biohaven Therapeutics, Ltd. (“Biohaven”) and Yale University (“Yale”) (collectively “Plaintiffs”) hereby provide the following amended disclosures. Plaintiffs reserves the right to modify, amend, retract, and/or supplement these disclosures.

I. Yale Custodians.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹ The “Asserted Trade Secrets” refer to the trade secrets identified in Plaintiffs’ October 27, 2023 “Identification of Trade Secrets.”

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

II. Biohaven Custodians.

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

III. Non-custodial ESI Data Sources

[REDACTED]

IV. Inaccessible Data Sources

At this this time, Plaintiffs do not believe there are any data sources likely to contain discoverable ESI that are not reasonably accessible under Fed. R. Civ. P. 26(b)(2)(C)(i). If Plaintiffs become aware of any such sources, Plaintiffs will promptly supplement their disclosures.

V. Third-Party Discovery

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Dated: November 21, 2023

FARNAN LLP

/s/ Brian E. Farnan

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Highly Confidential (Subject to the Protective Order [D.I. 65])

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Biohaven Therapeutics Ltd.

CERTIFICATE OF SERVICE

I, Brian E. Farnan, hereby certify that on November 21, 2023, a copy of Plaintiffs Biohaven Therapeutics, Ltd. and Yale University's Amended ESI Disclosures was served on the following as indicated:

Via E-Mail

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/s/ Brian E. Farnan

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EXHIBIT 31

From: Spiegel, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0835116661DB416199961B1ECE52169C-DS256]
Sent: 10/12/2022 9:45:40 PM
To: McDonald, David [david.mcdonald@yale.edu]
Subject: slides
Attachments: Chembiol_Retreat_Spiegel_2-1.pptx

Targeted Degradation of Extracellular Proteins



David A. Spiegel, MD, PhD
Chemical Biology Fall Retreat
October 14th, 2022

Spiegel Group

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

EXHIBIT 32

MODA

From: Reese Caldwell <reese.caldwell@biohavenpharma.com>
To: Donnie McGrath <donnie.mcgrath@biohavenpharma.com>
Cc: Gene Dubowchik <gene.dubowchik@biohavenpharma.com>
Date: Fri, 16 Oct 2020 14:36:14 -0400

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EXHIBIT 33

**IN THE UNITED STATES DISTRICT COURT
FOR DISTRICT OF DELAWARE**

BIOHAVEN THERAPEUTICS LTD.
and YALE UNIVERSITY,
Plaintiffs,

v.

AVILAR THERAPEUTICS, INC., a
Delaware corporation, RA CAPITAL
MANAGEMENT GP, LLC, a
Delaware corporation, and MILIND
DESHPANDE, an individual,
Defendants.

C.A. No. 1:23-cv-00328-CFC

**DEFENDANTS AVILAR THERAPEUTICS, INC. AND
RA CAPITAL MANAGEMENT GP, LLC'S
FIRST SET OF INTERROGATORIES TO PLAINTIFFS
BIOHAVEN THERAPEUTICS LTD. AND YALE UNIVERSITY**

Pursuant to Rules 26 and 33 of the Federal Rules of Civil Procedure, Defendants Avilar Therapeutics, Inc. and RA Capital Management GP, LLC request that Plaintiffs Biohaven Therapeutics Ltd. and Yale University provide written responses under oath to the following interrogatories (“Interrogatories”) within thirty (30) days of service. Each Interrogatory is to be read in accordance with the Definitions and Instructions that follow.

DEFINITIONS

1. These Definitions apply to all of the Instructions and Interrogatories below.

2. The term “Biohaven” means Biohaven Therapeutics Ltd., and its present and former directors, officers, professors, administrators, employees, predecessors in interest, successors in interest, servants, agents, attorneys, consultants, partners, associates, investigators, representatives, accountants, financial advisors, distributors, and any other person acting on their behalf, pursuant to their authority, or subject to their control.

3. The term “Yale” means Yale University, and its present and former directors, officers, professors, administrators, employees, predecessors in interest, successors in interest, servants, agents, attorneys, consultants, partners, associates, investigators, representatives, accountants, financial advisors, distributors, and any other person acting on their behalf, pursuant to their authority, or subject to their control. For clarity and not limitation, the term “Yale” includes Dr. Spiegel, the Spiegel Lab, Dr. Crews, and the Crews Lab, as those terms are defined herein.

4. The terms “Plaintiffs,” “You” and “Your” mean Biohaven and Yale, and their present and former directors, officers, professors, administrators, employees, predecessors in interest, successors in interest, servants, agents, attorneys, consultants, partners, associates, investigators, representatives, accountants, financial advisors, distributors, and any other person acting on their behalf, pursuant to their authority, or subject to their control. For clarity and not limitation, the terms “Plaintiffs,” “You” and “Your” include Dr. Spiegel, the Spiegel Lab, Dr. Crews, and the Crews Lab, as those terms are defined herein.

5. The term “Dr. Spiegel” means Yale Professor Dr. David A. Spiegel.

6. The term “Spiegel Lab” means the Yale laboratory headed by Yale Professor Dr. David A. Spiegel, including any undergraduate students, post-graduate students, and other university personnel who work within that laboratory.

7. The term “Dr. Crews” means Yale Professor Dr. Craig Crews.

8. The term “Crews Lab” means the Yale laboratory headed by Yale Professor Dr. Craig Crews, including any undergraduate students, post-graduate students, and other university personnel who work within that laboratory.

9. The term “Avilar” means Avilar Therapeutics, Inc., and its present and former directors, officers, professors, administrators, employees, predecessors in interest, successors in interest, servants, agents, attorneys, consultants, partners, associates, investigators, representatives, accountants, financial advisors, distributors, and any other person acting on their behalf, pursuant to their authority, or subject to their control.

10. The term “RA Capital” means RA Capital Management GP, LLC, and its present and former directors, officers, professors, administrators, employees, predecessors in interest, successors in interest, servants, agents, attorneys, consultants, partners, associates, investigators, representatives, accountants, financial advisors, distributors, and any other person acting on their behalf, pursuant to their authority, or subject to their control.

11. The term “Defendants” means Avilar and RA Capital, and their present and former directors, officers, employees, predecessors in interest, successors in interest, servants, agents, attorneys, consultants, partners, associates, investigators, representatives, accountants, financial advisors, distributors, and any other person acting on their behalf, pursuant to their authority, or subject to their control.

12. The terms “document” and “documents” have the broadest possible meaning under Rule 34(a) of the Federal Rules of Civil Procedure and include

“writing(s)” and “recording(s)” under Rule 1001 of the Federal Rules of Evidence, “tangible things” under Rules 26 and 34 of the Federal Rules of Evidence, and all of the following matter in Your actual or constructive possession, custody, or control: all written, typed, printed, recorded, textual, graphic or photographic matter, software, source code, and object code, however produced or reproduced, any notes or drafts, and all copies on which any mark, alteration, writing, or any other change from the original has been made.

13. The terms “communication” and “communications” mean any transmission of information between persons or entities by any means or medium, whether in original, draft, or copy form, whether stored in hard copy, on tape, or electronically, and whether oral or in writing, including: conversations; correspondence; electronic mails; telexes; facsimile transmissions; text messages; social media posts and chats; telecopies; recordings; telephone or message logs; voicemails; notes or memoranda; and any translations.

14. A document, thing, or communication “relating to,” “related to,” “relate to,” “referring to,” “refer to,” “concerning,” “associated with,” “connected with,” or “regarding” means all documents, things, or communications that directly or indirectly or in whole or in part constitute, contain, embody, concern, evidence, show, comprise, reflect, identify, state, refer to, report on, deal with, comment on, respond to, describe, involve, mention, discuss, record, address, analyze, support, negate, or are in any way pertinent to that subject.

15. The terms “person” and “persons” mean any individual, firm, association, organization, joint venture, partnership or corporation.

16. The terms “third party” and “third parties” mean any individual, firm, association, organization, joint venture, partnership or corporation other than Plaintiffs and Defendants.

17. The term “date” means the exact day, month and year, if ascertainable, or if not, Your best approximation thereof.

18. The terms “include,” “include,” and “including” mean include or including without limitation.

19. The term “any” shall include the word “all,” and vice versa.

20. The terms “and,” “or,” and “and/or” shall be construed conjunctively and disjunctively, whichever makes the discovery request more inclusive so as to bring within the scope of the request all documents and information that might otherwise be construed to be outside of its scope.

21. Singular forms of nouns and pronouns encompass their plural forms and vice versa, and any verbs encompass all tenses. Any pronoun shall be construed to refer to the masculine, feminine or neutral gender, as in each case is most appropriate.

22. The term “Complaint” means the sealed version of Plaintiffs’ Complaint in this action, filed March 24, 2023.

23. The term “Answer” means Defendants Avilar Therapeutics, Inc. and RA Capital Management GP, LLC’s First Amended Answer and Affirmative Defenses to Plaintiffs’ Complaint, filed June 30, 2023 (D.I. 27).

24. The terms “Confidential Disclosure Agreement” and “CDA” mean the Confidential Disclosure Agreement between Yale and RA Capital Management Group, LLC, effective April 10, 2019, a copy of which is attached as Exhibit 1 to the Complaint (D.I. 20-1).

25. The terms “Trade Secret” and “Trade Secrets” mean any item of non-public information Plaintiffs contend they treated as confidential, they disclosed to one or more Defendants in confidence, and one or more Defendants unlawfully used, disclosed or acquired such item.

26. The terms “Asserted Trade Secret” and “Asserted Trade Secrets” mean each of the alleged Trade Secrets identified by Plaintiffs in response to Interrogatory No. 1.

27. The term “identify with precision and specificity each and every alleged Trade Secret” means to provide a numbered list of each individual alleged Trade Secret (with each number constituting a separate Trade Secret) with a specific description of each such alleged Trade Secret in such a manner that the exact identity, scope, boundaries, constitutive elements, and content of each such alleged Trade Secret are fully disclosed in writing, in contrast to an agglomerated set of conclusory phrases that does not separately list and describe each such alleged Trade Secret, in contrast to a mere list of documents or file names, and with precision far above that required by any applicable pre-discovery Trade Secret claim identification requirement. If Plaintiffs contend that a particular combination of information constitutes an alleged Trade Secret, “identify with precision and specificity each and every alleged Trade Secret” shall also mean to identify the unique combination of information that Plaintiffs contend together constitutes an alleged Trade Secret.

28. The term “Spiegel Patent” means any patent or patent application (including unpublished provisional patent applications) regarding extracellular protein degradation in which Dr. Spiegel is listed as an inventor, including the following United States patent applications: 17046,221; 17654,984; 17654,990; 17695,259; 17768,145; and 17768,166.

29. The term “Yale Patent” means any patent or patent application (including unpublished provisional patent applications) regarding extracellular protein degradation assigned to Yale or in which any person affiliated with Yale is listed as an inventor.

30. The term “Biohaven Patent” means any patent or patent application (including unpublished provisional patent applications) regarding extracellular protein degradation assigned to Biohaven or in which any person affiliated with Biohaven is listed as an inventor.

INSTRUCTIONS

1. These Interrogatories are to be answered separately by each Plaintiff in writing under oath within thirty (30) days after the date of service hereof. If You acquire additional knowledge or information after answering the Interrogatories which requires supplementation of Your responses under the provisions of Fed. R. Civ. P. 26(e), it is requested that You supplement Your responses within ten (10) days after such additional knowledge or information is acquired.

2. These Interrogatories call for all information (including any information contained in or on any document) that is known or available to You, including all information in the possession of or available to Your attorneys, agents, employees, representatives, investigators or other persons who have or have obtained information on Your behalf.

3. With regard to each Interrogatory, should the answer require the identification of a person or entity, state the full name, last known residence, occupation, last known employer or business affiliation, last known title or business description, last known business address, last known telephone number, relationship to Plaintiffs or Defendants including all positions, employments or affiliations held by such person with Plaintiffs or Defendants and the dates such positions, employments or affiliations were held, and describe in detail all facts pertaining to the subject matter of this action known by each such person or entity.

4. With regard to each Interrogatory, should the answer require the identification of documents, provide a description of the documents and a citation to the unique production number(s) corresponding to such documents.

5. If documents are being produced in lieu of answers pursuant to Fed. R. Civ. P. 33(d), or if Your answer can be found in documents produced in response to a specific document request, identify, by document production number or similar means, the specific documents wherein the answer is located and, unless apparent on the face of the document, state where within the document the answer can be found.

6. If only a part of a discovery request is objectionable, the remainder of the request shall be answered. If an objection is made to an Interrogatory, or a part of an Interrogatory, the specific ground for the objection shall be set forth clearly in the response to that Interrogatory. As required by Fed. R. Civ. P. 33(b)(1), You shall answer each Interrogatory to the extent that it is not objectionable.

7. If any documents referred to in Your response to these Interrogatories were, but are no longer in Your possession, custody or control, state what disposition was made of them and when. If any document referred to in response to these Interrogatories has been lost or destroyed, state in detail the circumstances of such loss or destruction and identify each document lost or destroyed (and all files that contained such documents).

8. If, in responding to any of these Interrogatories, You encounter any ambiguity in construing either the Interrogatory or a Definition or Instruction relevant to it, You shall set forth the ambiguity and the construction selected or used in responding to the Interrogatory.

9. If You contend that any of these Interrogatories call for information protected by the attorney-client privilege, work product protection or any other claimed privilege, You shall state in Your objection the basis for any assertion of

privilege, shall identify the nature and general subject matter of any withheld information, document or communication and shall identify any communications and documents encompassed by the assertion of the privilege by stating the privilege being asserted, the date of said communication or document, the names of persons who were parties to the communication, and the purpose of the communication or document for which the privilege is claimed.

10. If, after conducting a reasonable investigation and exercising due diligence to secure the information requested, an individual Interrogatory or any part cannot be fully answered, You shall answer each Interrogatory to the fullest extent possible, state the extent of Your knowledge, the reasons for Your inability to fully answer, and all information, knowledge or belief You may have regarding the unanswered portion.

11. The Interrogatories shall be deemed continuing and if, after answering the Interrogatories, You acquire additional information or knowledge responsive to any of the Interrogatories, You are required to promptly provide supplementary responses to the Interrogatories as required by Fed. R. Civ. P. 26(e).

INTERROGATORIES

INTERROGATORY NO. 1:

Separately for each Defendant, identify with precision and specificity each and every alleged Trade Secret that Plaintiffs contend that Defendant unlawfully acquired, used, or disclosed.¹

INTERROGATORY NO. 2:

Separately for each Asserted Trade Secret, identify with precision and specificity every person and entity who participated in any way in the development or creation of the Asserted Trade Secret, the date(s) of such development or creation, the time and financial investment spent on such development or creation, and any documents memorializing or regarding such development or creation.

¹ The phrase “identify with precision and specificity each and every alleged Trade Secret” as used in Interrogatory No. 1 means to provide a numbered list of each individual such alleged Trade Secret (with each number constituting a separate Trade Secret) with a specific description of each such alleged Trade Secret in such a manner that the exact identity, scope, boundaries, constitutive elements, and content of each such alleged Trade Secret are fully disclosed in writing, in contrast to an agglomerated set of conclusory phrases that does not separately list and describe each such alleged Trade Secret, in contrast to a mere list of documents or file names, and with precision far above that required by any applicable pre-discovery Trade Secret claim identification requirement. If Plaintiffs contend that a particular combination of information constitutes an alleged Trade Secret, “identify with precision and specificity each and every alleged Trade Secret” shall also mean to identify the unique combination of constitutive elements that Plaintiffs contend together constitutes an alleged Trade Secret.

INTERROGATORY NO. 3:

Separately for each Asserted Trade Secret, identify with precision and specificity each and every measure taken by each Plaintiff to safeguard and keep secret the Asserted Trade Secrets from their creation until the present time, including the date(s) such measures were employed, all witnesses to such measures and any documents constituting, evidencing or memorializing such measures.

INTERROGATORY NO. 4:

Separately for each Asserted Trade Secret, identify with precision and specificity the independent economic value, if any, to each Plaintiff from each such Asserted Trade Secret not being generally known to, and not being readily ascertainable through proper means by, another person who can obtain economic value from the disclosure or use of the information.

INTERROGATORY NO. 5:

Separately for each Asserted Trade Secret, identify with precision and specificity every person or entity to whom Plaintiffs have ever disclosed such Asserted Trade Secret at any time (i.e., before or after the initiation of this lawsuit), including the date(s) of all such disclosures, all witnesses to each such disclosure and any documents constituting, evidencing or memorializing each such disclosure.

INTERROGATORY NO. 6:

Separately for each Asserted Trade Secret, identify with precision and specificity how Plaintiffs contend each Defendant received or otherwise obtained each Alleged Trade Secret, including the date(s) when Plaintiffs contend each Defendant received or obtained each Alleged Trade Secret, the exact means by which each Defendant received or obtained each Alleged Trade Secret, and any documents constituting, evidencing or memorializing such receipt.

INTERROGATORY NO. 7:

Separately for each Asserted Trade Secret that Plaintiffs contend Defendants used without Plaintiffs' authorization or consent, identify with precision and specificity each such alleged use and which Defendant(s) made the alleged use, including the exact information allegedly used, all date(s) of each such alleged unauthorized use, all place(s) of such unauthorized use, the identity of all person(s) who made each such unauthorized use, all witnesses to each such unauthorized use, the exact manner in which each such unauthorized use was effectuated and any documents constituting, evidencing or memorializing each such unauthorized use.

INTERROGATORY NO. 8:

Separately for each Asserted Trade Secret that Plaintiffs contend Defendants disclosed without Plaintiffs' authorization or consent, identify with precision and specificity each such alleged disclosure and which Defendant(s) made the alleged

disclosure, including the exact information allegedly disclosed, all date(s) of each such alleged unauthorized disclosure, all place(s) of such unauthorized disclosure, the identity of all person(s) who made each such unauthorized disclosure, all witnesses to each such unauthorized disclosure, the exact manner in which each such unauthorized disclosure was effectuated and any documents constituting, evidencing or memorializing each such unauthorized disclosure.

INTERROGATORY NO. 9:

Separately for each Asserted Trade Secret, identify with precision and specificity all facts in support of Your contention that such Asserted Trade Secret was neither generally known nor readily ascertainable by proper means.

INTERROGATORY NO. 10:

Separately for each Asserted Trade Secret, identify with precision and specificity whether such Asserted Trade Secret was ever included, disclosed or described in any Spiegel Patent, Yale Patent or Biohaven Patent, and identify with precision and specificity any Spiegel Patent, Yale Patent or Biohaven Patent which includes, discloses or describes such Asserted Trade Secret and where (by page number and, if applicable, line number) the Asserted Trade Secret is included, described or disclosed.

INTERROGATORY NO. 11:

With respect to Plaintiffs' cause of action for breach of contract, identify with precision and specificity all facts that Plaintiffs contend constitute a breach of the Confidential Disclosure Agreement, including the date(s) of each such breach, the specific provision(s) of the CDA breached, the conduct that constituted each such breach, the person(s) who participated in each such breach, the witness(es) to each such breach, and any documents constituting, evidencing or memorializing each such breach.

INTERROGATORY NO. 12:

State with specificity and precision the legal and factual bases for Your contention that the information shared by Dr. Spiegel or Yale with RA Capital pursuant to the Confidential Disclosure Agreement was not known to RA Capital prior to the disclosure by Dr. Spiegel or Yale, did not become publicly known through no fault or omission attributable to RA Capital, was not given to RA Capital by a third party under no obligation of confidentiality to Yale, or was not independently developed by RA Capital without the aid, application or use of the confidential information shared by Dr. Spiegel or Yale.

Dated: July 18, 2023

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CERTIFICATE OF SERVICE

I hereby certify that on the 18th day of July, 2023, a copy the foregoing document was served upon the following counsel via electronic mail.

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